



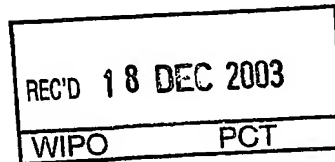
Re PCT/PTO

10/527866

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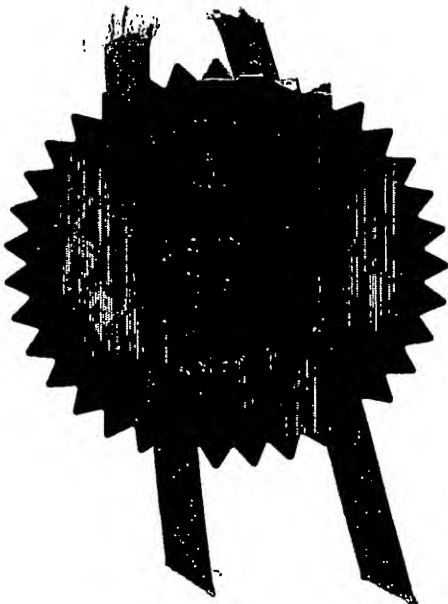
The Patent Office  
Concept House  
Cardiff Road  
Newport  
South Wales  
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

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Signed *AmBrewer*

Dated 6 August 2003



The  
Patent  
Office

1/77

# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office  
Cardiff Road  
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17SEP02 E748632-1 D02029  
P01/7700 0.00-0221455.9

1. Your reference

DMW/NM/P33108

2. Patent application number

(The Patent Office will fill in his part)

0221455.9

16 SEP 2002

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Patents ADP number (*if you know it*)

If the applicant is a corporate body, give the country/state of its incorporation

Glaxo Group Limited  
Glaxo Wellcome House, Berkeley Avenue,  
Greenford, Middlesex UB6 0NN, Great Britain

United Kingdom

50206457002

4. Title of the invention

Compounds

5. Name of your agent (*if you have one*)

"Address for service" in the United Kingdom to which all correspondence should be sent (*including the postcode*)

Patents ADP number (*if you know it*)

Corporate Intellectual Property

GlaxoSmithKline  
Corporate Intellectual Property (CN9 25.1)  
980 Great West Road  
BRENTFORD  
Middlesex TW8 9GS

7960982003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (*if you know it*) the or each application number

Country Priority application number Date of filing  
(*if you know it*) (*day / month / year*)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application Date of filing  
(*day / month / year*)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (*Answer yes if:*

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is named as an applicant, or
- c) any named applicant is a corporate body

See note (d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form.  
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|                                  |    |
|----------------------------------|----|
| Continuation sheets of this form | 0  |
| Description                      | 57 |
| Claim(s)                         | 0  |
| Abstract                         | 0  |
| Drawings                         | 0  |

3

10. If you are also filing any of the following, state how many against each item.

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

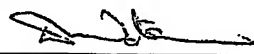
Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

P23/77

11.

We request the grant of a patent on the basis of this application

Signature  Date 16-Sep-02

D M Waters

12. Name and daytime telephone number of person to contact in the United Kingdom

D M Waters 01279 644283

Warning

*After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.*

Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered 'Yes' Patents Form 7/77 will need to be filed.
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## COMPOUNDS

The present invention relates to pyrazolopyridine compounds, processes for their preparation, intermediates usable in these processes, and pharmaceutical compositions containing the compounds. The invention also relates to the use of the pyrazolopyridine compounds in therapy, for example as inhibitors of phosphodiesterases and/or for the treatment and/or prophylaxis of inflammatory and/or allergic diseases such as chronic obstructive pulmonary disease (COPD), asthma or allergic rhinitis.

US 3,979,399, US 3,840,546, and US 3,966,746 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxamides wherein the 4-amino group NR<sub>3</sub>R<sub>4</sub> can be an acyclic amino group wherein R<sub>3</sub> and R<sub>4</sub> may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR<sub>3</sub>R<sub>4</sub> can alternatively be a 3-6-membered heterocyclic group such as pyrrolidino, piperidino and piperazino. The compounds are disclosed as central nervous system depressants useful as ataractic, analgesic and hypotensive agents.

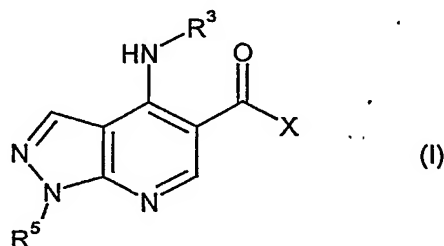
US 3,925,388, US 3,856,799, US 3,833,594 and US 3,755,340 (E.R.Squibb & Sons) disclose 4-amino derivatives of pyrazolo[3,4-b]pyridine-5-carboxylic acids and esters. The 4-amino group NR<sub>3</sub>R<sub>4</sub> can be an acyclic amino group wherein R<sub>3</sub> and R<sub>4</sub> may each be hydrogen, lower alkyl (e.g. butyl), phenyl, etc.; NR<sub>3</sub>R<sub>4</sub> can alternatively be a 5-6-membered heterocyclic group in which an additional nitrogen is present such as pyrrolidino, piperidino, pyrazolyl, pyrimidinyl, pyridazinyl or piperazinyl. The compounds are mentioned as being central nervous system depressants useful as ataractic agents or tranquilisers, as having antiinflammatory and analgesic properties. The compounds are mentioned as increasing the intracellular concentration of adenosine-3',5'-cyclic monophosphate and for alleviating the symptoms of asthma.

EP 0 076 035 A1 (ICI Americas) discloses pyrazolo[3,4-b]pyridine derivatives as central nervous system depressants useful as tranquilisers or ataractic agents for the relief of anxiety and tension states.

The compound cartazolate is known (ethyl 1-ethyl-4-n-butylamino-1H-pyrazolo[3,4-b]pyridine-5-carboxylate). J.W. Daly et al., *Med. Chem. Res.*, 1994, 4, 293-306 and D. Shi et al., *Drug Development Research*, 1997, 42, 41-56 disclose a series of 4-(amino)substituted 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid derivatives and their affinities at A<sub>1</sub>- and A<sub>2A</sub>-adenosine receptors, and the latter paper discloses their affinities at various binding sites of the GABA<sub>A</sub>-receptor channel. S. Schenone et al., *Bioorg. Med. Chem. Lett.*, 2001, 11, 2529-2531 disclose a series of 4-amino-1-(2-chloro-2-phenylethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl esters as A<sub>1</sub>-adenosine receptor ligands.

It is desirable to find new compounds which bind to, and preferably inhibit, phosphodiesterase type IV (PDE4).

- 5 The present invention provides a compound of formula (I) or a salt thereof (in particular, a pharmaceutically acceptable salt thereof):

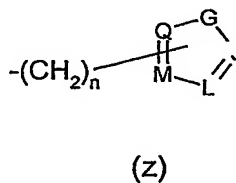
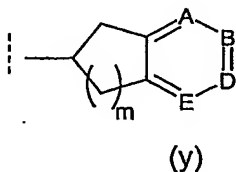
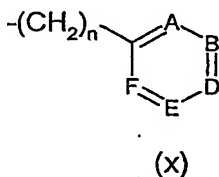


wherein:

- 10 X is  $\text{NR}^1\text{R}^2$  or  $\text{OR}^{2a}$ , in which:

$\text{R}^1$  is hydrogen,  $\text{C}_{1-2}$ alkyl or  $\text{C}_{1-2}$ fluoroalkyl, and

- 15  $\text{R}^2$  is hydrogen,  $\text{C}_{1-8}$ alkyl,  $\text{C}_{1-8}$  fluoroalkyl, or  $\text{C}_{3-8}$ cycloalkyl, phenyl optionally substituted with one or two of: a halogen atom,  $\text{C}_{1-2}$ alkyl, trifluoromethyl,  $\text{C}_{1-2}$ alkoxy or trifluoromethoxy; or  $\text{R}^2$  has the sub-formula (x), (y) or (z):



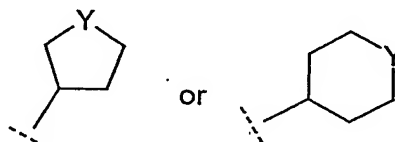
- 20 wherein in sub-formula (x) and (z),  $n = 1$  or  $2$ ; and in sub-formula (y),  $m = 1$  or  $2$ ;  
 wherein in sub-formula (x) and (y), none, one or two of A, B, D, E and F are nitrogen; and the remaining of A, B, D, E and F are CH or  $\text{CR}^6$  where  $\text{R}^6$  is a halogen atom,  $\text{C}_{1-4}$ alkyl,  $\text{C}_{1-4}$ fluoroalkyl,  $\text{C}_{1-2}$ alkoxy,  $\text{C}_{1-2}$ fluoroalkoxy,  $\text{C}_{1-2}$ alkylsulphonyl ( $\text{C}_{1-2}$ alkyl- $\text{SO}_2$ -),  $\text{C}_{1-2}$ alkyl- $\text{SO}_2$ -NH-,  $\text{R}^7\text{R}^8\text{N-SO}_2$ -,  $\text{R}^7\text{R}^8\text{N-CO-}$ ,  $\text{R}^7\text{R}^8\text{N}$ , OH,  
 25  $\text{C}_{1-4}$ alkoxymethyl, or  $\text{C}_{1-2}$ alkyl- $\text{SO}_2$ - $\text{CH}_2$ -, wherein  $\text{R}^7$  and  $\text{R}^8$  are independently hydrogen or  $\text{C}_{1-2}$ alkyl;

wherein in sub-formula (z), G is O or S or  $\text{NR}^9$  wherein  $\text{R}^9$  is  $\text{C}_{1-4}$ alkyl or  $\text{C}_{1-4}$ fluoroalkyl; none, one or two of J, L, M and Q are nitrogen; and the remaining of J, L, M and Q are CH or  $\text{CR}^6$  where  $\text{R}^6$  is as defined herein;

30 or  $\text{R}^1$  and  $\text{R}^2$  taken together are  $-(\text{CH}_2)_p-$  where  $p = 3, 4$  or  $5$  (preferably  $p = 4$ );

R<sup>2a</sup> is C<sub>1-8</sub>alkyl; C<sub>1-8</sub> fluoroalkyl; C<sub>3-8</sub>cycloalkyl; phenyl optionally substituted with one or two of: a halogen atom, C<sub>1-2</sub>alkyl, trifluoromethyl, C<sub>1-2</sub>alkoxy or trifluoromethoxy; or R<sup>2a</sup> has the sub-formula (x), (y) or (z) as defined herein;

5



R<sup>3</sup> is C<sub>3-8</sub>cycloalkyl or a heterocyclic group being in which Y is O, S, SO<sub>2</sub>, or NR<sup>10</sup>; where R<sup>10</sup> is hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-2</sub>fluoroalkyl, C(O)-C<sub>1-2</sub>alkyl, or C(O)-CF<sub>3</sub>;

10 and wherein in R<sup>3</sup> the C<sub>3-8</sub>cycloalkyl or heterocyclic group is optionally substituted with one or two substituents being OH, C<sub>1-2</sub>alkoxy, trimethoxy, or C<sub>1-2</sub>alkyl group; and wherein any OH, alkoxy or trimethoxy substituent is not substituted at the ring carbon attached to the -NH- group of formula (I) and is not substituted at either ring carbon bonded to the Y group of the heterocyclic group; and

15

R<sup>5</sup> = hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-2</sub>fluoroalkyl, phenyl or benzyl.

Preferably, where X is OR<sup>2a</sup>, the compound is other than the compound wherein R<sup>5</sup> is methyl, X is OEt, and R<sup>3</sup> is cyclopentyl.

20

In compounds, for example in the compounds of formula (I), an "alkyl" group or moiety may be straight or branched. Alkyl groups which may be employed include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl and any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, isobutyl, 2-ethylbutan-1-yl, and the like.

25

A corresponding meaning is intended for "alkoxy", "alkylene", and like terms derived from alkyl. For example, "alkoxy" such as C<sub>1-6</sub>alkoxy or C<sub>1-4</sub>alkoxy includes methoxy, ethoxy, propyloxy, and oxy derivatives of the alkyls listed above.

"Alkylsulfonyl" such as C<sub>1-4</sub>alkylsulfonyl includes methylsulfonyl (methanesulfonyl),

30

ethylsulfonyl, and others derived from the alkyls listed above. "Alkylsulfonyloxy" such as C<sub>1-4</sub>alkylsulfonyloxy includes methanesulfonyloxy (methylsulfonyloxy), ethanesulfonyloxy, *et al.*

"Cycloalkyl", for example C<sub>3-8</sub>cycloalkyl, includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. Preferably, a C<sub>3-8</sub>cycloalkyl group is C<sub>3-6</sub>cycloalkyl or C<sub>5-6</sub>cycloalkyl, that is contains a 3-6 membered or 5-6 membered carbocyclic ring.

35

"Fluoroalkyl" includes alkyl groups with one, two, three, four, five or more fluorine substituents, for example monofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, etc. "Fluoroalkoxy" includes trifluoromethoxy, pentafluoroethoxy, monofluoromethoxy, difluoromethoxy, etc. "Fluoroalkylsulfonyl" such as C<sub>1-4</sub>fluoroalkylsulfonyl includes trifluoromethanesulfonyl, pentafluoroethylsulfonyl, etc.

A halogen atom present in compounds, for example in the compounds of formula (I), may be fluorine, chlorine, bromine or iodine.

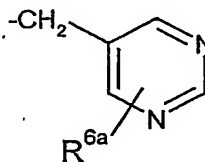
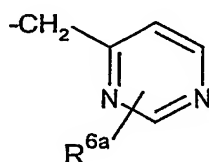
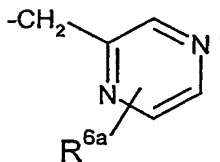
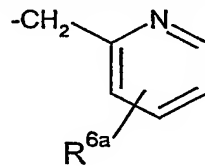
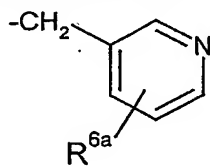
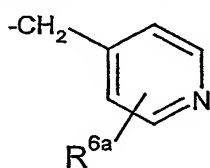
Preferably, X is NR<sup>1</sup>R<sup>2</sup>.

When or R<sup>2</sup> has the sub-formula (x) or (y) or (z), preferably R<sup>2</sup> has the sub-formula (x) or (y), more preferably (x).

In sub-formula (x) and/or (y), it is preferred that none, one or two of A, B, D, E and F are nitrogen; none, one, two or three of A, B, D, E and F are CR<sup>6</sup>; and the remaining of A, B, D, E and F are CH. More preferably, none, one or two of A, B, D, E and F are nitrogen; none or one of A, B, D, E and F are CR<sup>6</sup>; and the remaining of A, B, D, E and F are CH.

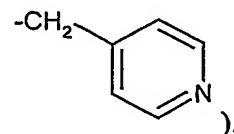
In sub-formula (x) and/or (y), preferably, none or one of A, B, D, E and F are nitrogen, and/or preferably none of A, B, D, E and F are CR<sup>6</sup>.

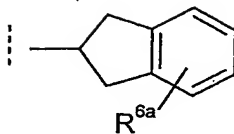
Preferably, sub-formula (x) is: benzyl; phenethyl (Ph-C<sub>2</sub>H<sub>4</sub>-); benzyl or phenethyl being substituted on the phenyl ring with a single R<sup>6</sup> substituent, or one of the following:



, wherein R<sup>6a</sup> is either R<sup>6</sup> as defined herein or (preferably) hydrogen.

Most preferably, sub-formula (x) is benzyl or pyridin-4-ylmethyl (i.e.





Preferably, sub-formula (y) is:  
herein or preferably hydrogen.

, wherein  $R^{6a}$  is either  $R^6$  as defined

5 In sub-formula (x), (y) and (z), preferably,  $R^6$  is a fluorine or chlorine atom, methyl, ethyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, methyl-SO<sub>2</sub>-NH-, Me<sub>2</sub>N-SO<sub>2</sub>-, -CONH<sub>2</sub>, -CONHMe, NMe<sub>2</sub>, t-butoxymethyl, or methyl-SO<sub>2</sub>-CH<sub>2</sub>-. More preferably,  $R^6$  is a fluorine or chlorine atom, methyl, trifluoromethyl, methoxy, methyl-SO<sub>2</sub>-NH-, Me<sub>2</sub>N-SO<sub>2</sub>- or -CONH<sub>2</sub>.

10 In sub-formula (x) and/or (y), preferably, any  $R^6$  substituent is present only in B, D and/or E, so that in sub-formula (x) any  $R^6$  substituent is present only in the meta- (3-) and/or para- (4-) positions with respect to the -(CH<sub>2</sub>)<sub>n</sub>- side-chain.

15 Overall for  $R^2$ , it is preferable that  $R^2$  is hydrogen, C<sub>1-6</sub>alkyl (e.g. C<sub>3-6</sub>alkyl), C<sub>1-4</sub>fluoroalkyl, C<sub>3-6</sub>cycloalkyl (e.g. C<sub>5-6</sub>cycloalkyl), phenyl optionally substituted with one of: a fluorine or chlorine atom, methyl, trifluoromethyl, methoxy or trifluoromethoxy; or  $R^2$  has the sub-formula (x), (y) or (z), for example as described above; or  $R^1$  and  $R^2$  taken together are -(CH<sub>2</sub>)<sub>p</sub>- where p = 4 or 5.

20 Still more preferably,  $R^2$  is hydrogen, methyl, ethyl, n-propyl, iso-propyl, 2-ethylbutan-1-yl, cyclopentyl, cyclohexyl, fluorophenyl e.g. 4-fluorophenyl, benzyl, or pyridin-4-ylmethyl; or  $R^1$  and  $R^2$  taken together are -(CH<sub>2</sub>)<sub>p</sub>- where p = 4. Most preferably,  $R^2$  is benzyl, pyridin-4-ylmethyl, or 4-fluorophenyl.

25 (Similar preferences apply for  $R^{2a}$  as for  $R^2$ , except that  $R^{2a}$  cannot be hydrogen. Most preferably,  $R^{2a}$  is ethyl.)

Preferably,  $R^1$  is hydrogen.

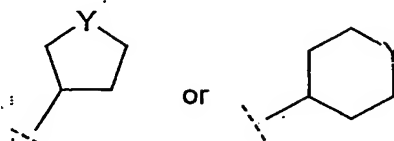
30 Preferably,  $R^5$  is C<sub>1-4</sub>alkyl or C<sub>1-2</sub>fluoroalkyl; more preferably C<sub>1-4</sub>alkyl; still more preferably methyl or ethyl; most preferably ethyl.

35 Preferably, where  $R^3$  is C<sub>3-8</sub>cycloalkyl, it is not C<sub>5</sub>cycloalkyl, i.e. not cyclopentyl. More preferably, where  $R^3$  is C<sub>3-8</sub>cycloalkyl, it is C<sub>6</sub>cycloalkyl (i.e. cyclohexyl) optionally substituted with one or two substituents being OH, C<sub>1-2</sub>alkoxy, trimethoxy, or C<sub>1-2</sub>alkyl group, and wherein any OH, alkoxy or trimethoxy substituent is not substituted at the  $R^3$



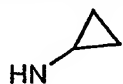
ring carbon attached to the -NH- group of formula (I). Where  $R^3$  is  $C_{3-8}$ cyclohexyl,  $R^3$  is most preferably cyclohexyl (i.e. unsubstituted).

- 5 Where  $R^3$  is the heterocyclic group being preferably Y is O, S,  $SO_2$ , NMe or N-C(O)methyl.

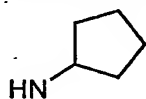


Preferably, in  $R^3$  the  $C_{3-8}$ cycloalkyl or heterocyclic group is unsubstituted.

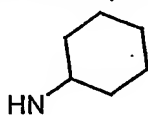
- 10 Preferably,  $NHR^3$  is of sub-formula (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), or (L):



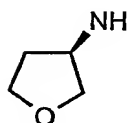
(a)



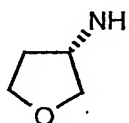
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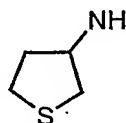
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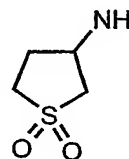
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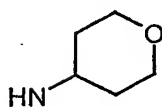
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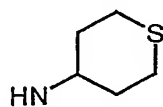
(f)



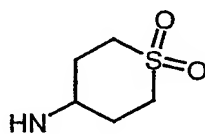
(g)



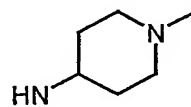
(h)



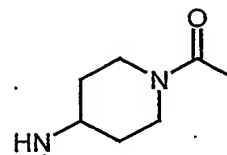
(i)



(j)



(k)



(L)

Most preferably,  $R^3$  is tetrahydro-2H-pyran-4-yl; that is  $NHR^3$  is most preferably of sub-formula (h), shown above.

15

It is most preferred that the compound of formula (I) or the salt thereof is:

- Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 20 Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 4-[(1-methylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 4-[(1-acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,

- Ethyl 4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate;  
 Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 5 Ethyl 1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 10 Ethyl 4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 4-(cyclopentylamino)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 1-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate;  
 Ethyl 4-(cyclopentylamino)-1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 15 Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 4-(cyclopentylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate,  
 N-Benzyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 20 1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 N-Cyclopentyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 4-(Cyclohexylamino)-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 N-Cyclopentyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 25 N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 30 N-Cyclopentyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridine-4-amine,  
 N-Cyclohexyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridine-4-amine,  
 1-Ethyl-5-(pyrrolidin-1-ylcarbonyl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridine-4-amine,  
 4-(Cyclopentylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 35 4-(Cyclohexylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 1-Ethyl-N-(pyridin-4-ylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 40 4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 4-(Cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

- 1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
N-Benzyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
N-Benzyl-4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
5 4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-(Cyclopentylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-(Cyclohexylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
1-Ethyl-N-(2-ethylbutyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-  
carboxamide,  
10 1-Ethyl-N-(2-ethylbutyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-  
carboxamide,  
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-  
carboxamide,  
4-(Cyclopentylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
15 4-(Cyclohexylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
1-Ethyl-N-(4-fluorophenyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-  
carboxamide,  
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-  
carboxamide,  
20 4-(Cyclopentylamino)-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-(Cyclohexylamino)-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
1-Ethyl-N-n-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-  
carboxamide,  
1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-  
25 carboxamide,  
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-  
carboxamide,  
N-Benzyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-  
30 carboxamide,  
1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-  
5-carboxamide,  
N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-  
carboxamide,  
35 4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-  
carboxamide,  
N-Benzyl-4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
N-Benzyl-4-(cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
N-Benzyl-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-  
40 carboxamide,  
4-(Cyclopentylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-(Cyclohexylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

- N-(2-Ethylbutyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-(Cyclopentylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-(Cyclohexylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
5 N-(4-Fluorophenyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-(Cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-(Cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
1-Methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
10 N-Benzyl-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
N-(2-Ethylbutyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
15 4-[(1-Acetylpiperidin-4-yl)amino]-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
N-(4-Fluorophenyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
20 4-[(1-Acetylpiperidin-4-yl)amino]-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
1-Methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
4-[(1-Acetylpiperidin-4-yl)amino]-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
1-Ethyl-N-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
25 1-Ethyl-N,N-dimethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
1-Ethyl-N-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
1-Ethyl-N-isopropyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
30 N-Benzyl-1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
N-Benzyl-1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
35 N-Benzyl-1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
N-Benzyl-4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
N-Benzyl-4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
N-Benzyl-4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,  
40 N-Benzyl-1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

1-Ethyl-N-(4-fluorophenyl)-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

1-Ethyl-N-(4-fluorophenyl)-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

5 1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

4-(Cyclopropylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide,

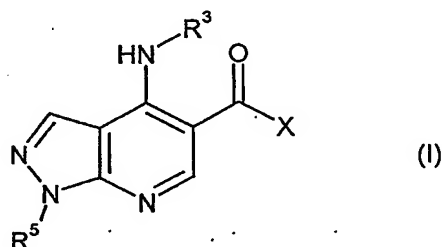
10 4-[(1,1-Dioxidotetrahydrothien-3-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide, or

4-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

15 or a salt thereof, e.g. a pharmaceutically acceptable salt thereof.

### Synthetic Process Routes

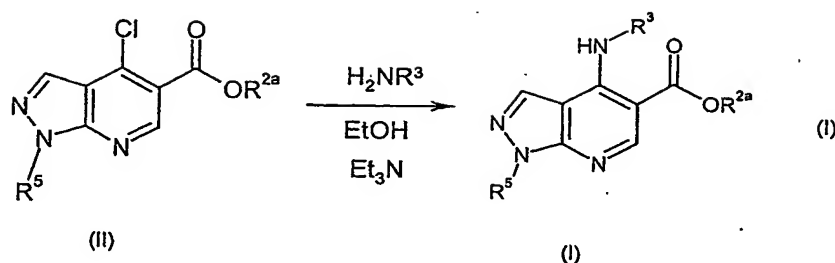
The following processes can be used to make the compounds of the invention:



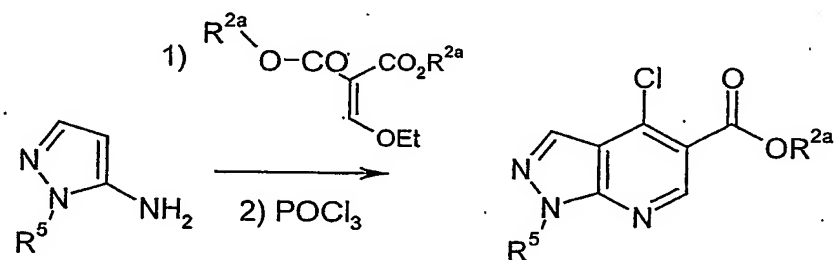
### Process A

25 Compounds of formula (I) where  $X = OR^{2a}$ , can be prepared according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027, by reaction of a compound of formula (II) with an amine of formula  $R^3NH_2$ . The reaction is preferably carried out in the presence of a base such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, dioxane or acetonitrile. The reaction may require heating

30 e.g. to ca. 60-100 °C, for example ca. 80-90 °C:



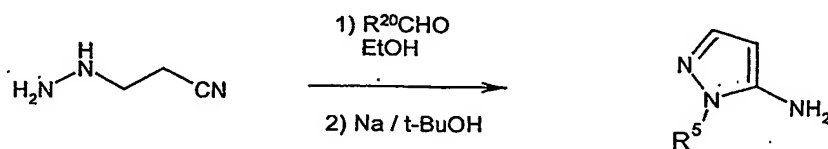
- Compounds of formula (II) are also described in the above reference and can be prepared by reaction of a compound of formula (III) with, for example, diethylethoxymethylene malonate (where  $R^{2a} = \text{Et}$ ) with heating, followed by reaction with phosphorous oxychloride, again with heating:



Formula III

Formula II

- Where the desired amino pyrazole of formula (III) is not commercially available (for example  $R^5 = \text{CH}_2\text{Ph}$ ), preparation can be achieved using methods described by Dorgan et. al. in J. Chem. Soc., Perkin Trans. 1, (4), 938-42; 1980, by reaction of cyanoethylhydrazine with a suitable aldehyde of formula  $R^{20}\text{CHO}$  in a solvent such as ethanol, with heating, followed by reduction with, for example sodium in a solvent such as t-butanol.  $R^{20}$  should be chosen so as to contain one less carbon atom than  $R^5$ , for example  $R^{20} = \text{methyl}$  will afford  $R^5 = \text{ethyl}$ .

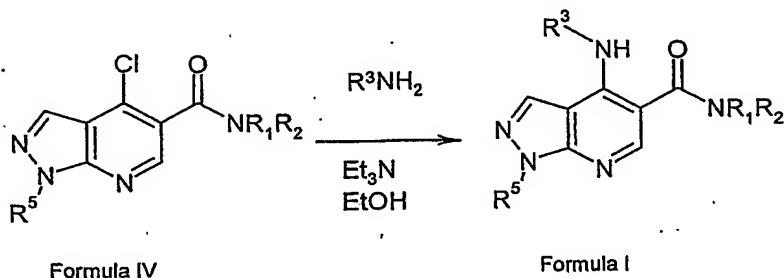


Formula III

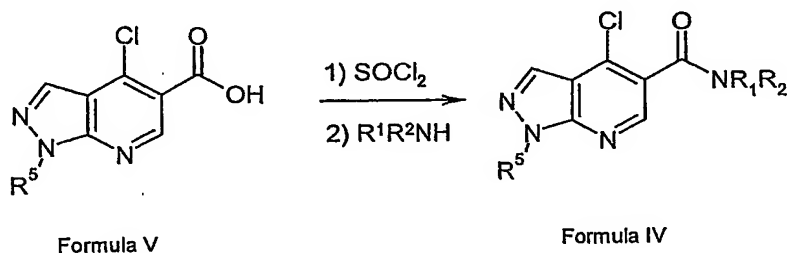
### Process B

Compounds of formula (I) where  $X = \text{NR}^1\text{R}^2$ , can be prepared by reaction of a compound of formula (IV) with an amine of formula  $\text{R}^3\text{NH}_2$ . The reaction is preferably carried out in the presence of a base, such as triethylamine or N,N-diisopropylethylamine, and/or in an organic solvent such as ethanol, THF, dioxane or acetonitrile. The reaction

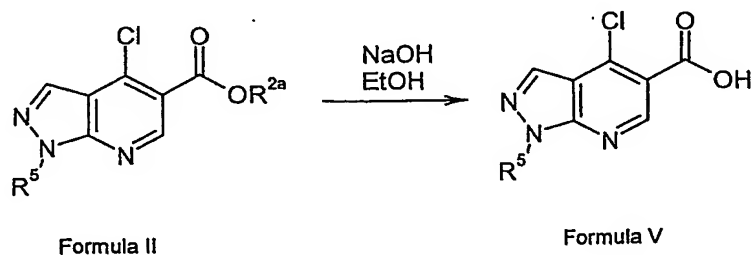
may require heating, e.g. to ca. 60-100 °C or ca. 80-90 °C, for example for 8-48 or 12-24 hours:



- 5 Compounds of formula (IV) can be prepared in a two step procedure as described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573. This process involves, first, reaction of a compound of formula (V) with thionyl chloride (or another agent suitable for forming an acid chloride from a carboxylic acid), either in an organic solvent such as chloroform or THF, or as a neat solution. This reaction may require heating and the thus-formed
- 10 intermediate may or may not be isolated. Step two involves reaction with an amine of formula  $R^1R^2NH$ , in an organic solvent such as THF or chloroform and may also involve the use of a base such as triethylamine or diisopropylethyl amine:

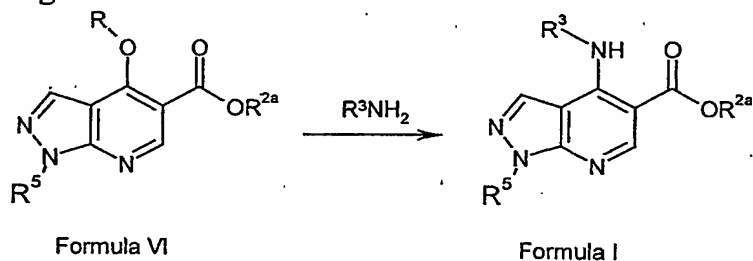


- 15 Compounds of formula (V) can be prepared by hydrolysis of an ester of formula (II) according to the method described by Yu et. al. in *J. Med Chem.*, 2001, 44, 1025-1027. This procedure preferably involves reaction with a base such as sodium hydroxide or potassium hydroxide in a solvent e.g. an aqueous solvent such as aqueous ethanol or
- 20 aqueous dioxane:

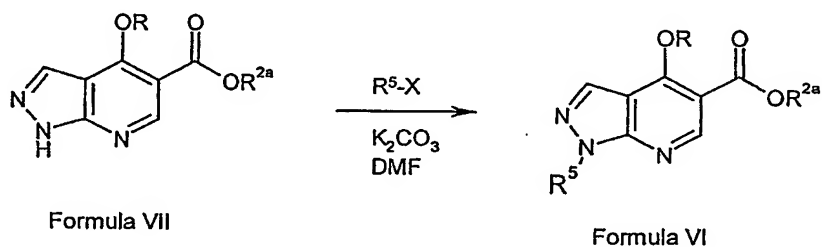


### Process C

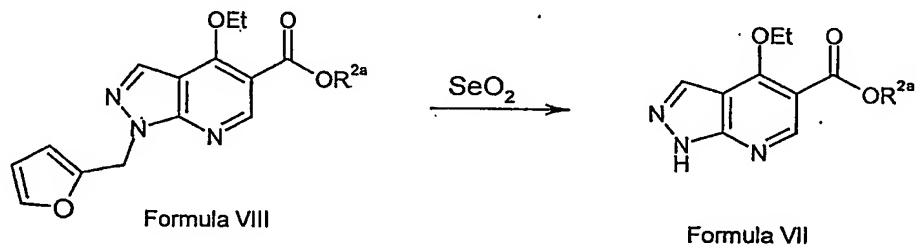
Compounds of formula (I) can also be prepared according to the method described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573, which involves reaction of a compound of formula (VI), in which -O-R is -O-C<sub>1-4</sub>alkyl, in particular -O-Et, with an amine of formula R<sup>3</sup>NH<sub>2</sub>. The reaction may be carried out with or without solvent and may require heating.



Compounds of formula (VI) (also described in the above reference) can be prepared by reaction of a compound of formula (VII) with a suitable alkylating agent of formula  $R^5-X$ , where X is a leaving group such as halogen. The reaction should be carried out in the presence of a base such as potassium carbonate, in an anhydrous solvent such as DMF:



The preparation of compounds of formula VII by oxidative cleavage of compounds of formula VIII is described by Bare et. al. in *J. Med. Chem.* 1989, 32, 2561-2573 (further referred to Zuleski et. al. in *J. Drug. Metab. Dispos.*, 1985, 13,139).



### Process D:

To form a compound of formula (I) wherein  $X = NR^1R^2$ , a compound of formula (I) but wherein  $X = OH$  (a carboxylic acid) can be converted into an activated compound of formula (I) but wherein  $X =$  a leaving group substitutable by an amine; and subsequently the activated compound can be reacted with an amine of formula  $R^3NH_2$ . For example,



the activated compound can be the acid chloride i.e. an activated compound of formula (I) but wherein  $X = Cl$ . This can be formed from the carboxylic acid ( $X = OH$ ) e.g. by thionyl chloride. See for example Examples 81-85.

5

The present invention therefore also provides a method of preparing a compound of formula (I) or a salt thereof, comprising :

10

(a) for a compound of formula (I) wherein  $X = OR^{2a}$ , reaction of a compound of formula (II) with an amine of formula  $R^3NH_2$ , or

(b) for a compound of formula (I) wherein  $X = NR^1R^2$ , reaction of a compound of formula (IV) with an amine of formula  $R^3NH_2$ , or

15

(c) reaction of a compound of formula (VI), in which  $-O-R$  is  $-O-C_{1-4}alkyl$ , with an amine of formula  $R^3NH_2$ ;

20

(d) to form a compound of formula (I) wherein  $X = NR^1R^2$ , conversion of a compound of formula (I) but wherein  $X = OH$  (a carboxylic acid) into an activated compound of formula (I) but wherein  $X =$  a leaving group substitutable by an amine (preferably, the activated compound can be the acid chloride i.e. an activated compound of formula (I) but wherein  $X = Cl$ ), and subsequent reaction of the activated compound with an amine of formula  $R^3NH_2$ ;

25

and optionally converting the compound of formula (I) into a salt e.g. a pharmaceutically acceptable salt.

### Medical uses

30

The present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance in a mammal such as a human. The compound or salt can be for use in the treatment and/or prophylaxis of any of the conditions described herein and/or for use as a phosphodiesterase inhibitor e.g. for use as a phosphodiesterase 4 (PDE4) inhibitor. "Therapy" may include treatment and/or prophylaxis.

35

40

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (e.g. pharmaceutical composition) for the treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal such as a human.

Also provided is a method of treatment and/or prophylaxis of an inflammatory and/or allergic disease in a mammal (e.g. human) in need thereof, which comprises administering to the mammal (e.g. human) a therapeutically effective amount of a compound of formula (I) as herein defined or a pharmaceutically acceptable salt thereof.

Phosphodiesterase 4 inhibitors are thought to be useful in the treatment and/or prophylaxis of a variety of diseases, especially inflammatory and/or allergic diseases, in mammals such as humans, for example: asthma, chronic bronchitis, emphysema, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock, adult respiratory distress syndrome, or multiple sclerosis.

In the treatment and/or prophylaxis, the inflammatory and/or allergic disease is preferably chronic obstructive pulmonary disease (COPD), asthma, or allergic rhinitis in a mammal (e.g. human). More preferably, the treatment and/or prophylaxis is of COPD or asthma in a mammal (e.g. human). PDE4 inhibitors are thought to be effective in the treatment of asthma (e.g. see M.A.Giembycz, *Drugs*, Feb. 2000, 59(2), 193-212; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; and refs cited therein) and COPD (e.g. see S.L. Wolda, *Emerging Drugs*, 2000, 5(3), 309-319; Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438; and refs cited therein). COPD is often characterised by the presence of airflow obstruction due to chronic bronchitis and/or emphysema (SL Wolda, 2000).

#### Pharmaceutical compositions and dosing

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers and/or excipients.

The pharmaceutical composition can be for use in the treatment and/or prophylaxis of any of the conditions described herein.

The compounds of formula (I) and/or the pharmaceutical composition may be administered, for example, by oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. Accordingly, the pharmaceutical composition is preferably suitable for oral, parenteral (e.g. intravenous, subcutaneous, or intramuscular), inhaled or nasal administration. More preferably, the pharmaceutical composition is suitable for inhaled or oral administration, e.g. to a mammal such as a

human. Inhaled administration involves topical administration to the lung e.g. by aerosol or dry powder composition. Oral administration to a human is most preferred.

5 A pharmaceutical composition suitable for oral administration can be liquid or solid; for example it can be a syrup, suspension or emulsion, a tablet, a capsule or a lozenge.

10 A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutically acceptable liquid carrier(s), for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

15 A pharmaceutical composition suitable for oral administration being a tablet can comprise one or more pharmaceutically acceptable carriers and/or excipients suitable for preparing tablet formulations. Examples of such carriers include lactose and cellulose. The tablet can also or instead contain one or more pharmaceutically acceptable excipients, for example binding agents, lubricants such as magnesium stearate, and/or tablet disintegrants.

20 A pharmaceutical composition suitable for oral administration being a capsule can be prepared using encapsulation procedures. For example, pellets containing the active ingredient can be prepared using a suitable pharmaceutically acceptable carrier and then filled into a hard gelatin capsule. Alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutically acceptable carrier, for example an aqueous gum or an oil and the dispersion or suspension then filled into a soft gelatin capsule.

25 A parenteral composition can comprise a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil. Alternatively, the solution can be lyophilised; the lyophilised parenteral pharmaceutical composition can be reconstituted with a suitable solvent just prior to administration.

30 Compositions for nasal or inhaled administration may conveniently be formulated as aerosols, drops, gels or dry powders.

35 Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

40 Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide, or an organic propellant such as a chlorofluorocarbon (CFC) or hydrofluorocarbon (HFC). Suitable CFC propellants include dichlorodifluoromethane, trichlorofluoromethane and dichlorotetrafluoroethane. Suitable HFC propellants include 1,1,1,2,3,3,3-

heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser.

Preferably, a pharmaceutical composition for inhaled administration is incorporated into a plurality of sealed dose containers mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable on demand and the dose administered by inhalation via the device such as the DISKUS™ device, marketed by GlaxoSmithKline.

Preferably the composition is in unit dose form such as a tablet or capsule for oral administration.

In the pharmaceutical composition, each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. Each dosage unit for nasal or inhaled administration preferably contains from 0.001 to 50 mg, more preferably 0.01 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds or salts of the invention can be administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day or 0.5 to 1000 mg per day, or a nasal or inhaled dose of 0.001 to 50 mg per day or 0.01 to 5 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

## Biological Test Methods

### PDE 3, PDE 4B, PDE 5 Primary assay methods

The activity of the compounds can be measured in the shown below. Preferred compounds of the invention are selective PDE4 inhibitors, i.e. they inhibit PDE4 (e.g. PDE4B and/or PDE4D) more strongly than they inhibit PDE3 and/or more strongly than they inhibit PDE5.

#### *Human recombinant PDE4B*

Human recombinant PDE4B is disclosed in WO 94/20079 and also M.M. McLaughlin et al., A low  $K_m$ , rolipram-sensitive, cAMP-specific phosphodiesterase from human brain: cloning and expression of cDNA, biochemical characterisation of recombinant protein, and tissue distribution of mRNA, *J. Biol. Chem.*, 1993, 268, 6470-6476). Human recombinant PDE4B was expressed in the PDE-deficient yeast *Saccharomyces cerevisiae* strain GL62. 100,000 x g supernatant fractions of yeast cell lysates were used for PDE4B assays and inhibitor studies.

#### *Inhibition of PDE 3, PDE 4B, or PDE 5 activity*

The ability of compounds to inhibit catalytic activity at PDE4B (human recombinant), PDE3 (from bovine aorta) or PDE5 (human recombinant) was determined by Scintillation Proximity Assay (SPA) in 96-well format. Test compounds were preincubated at ambient temperature in Wallac Isoplates (code 1450-514) with PDE enzyme in 50mM Tris-HCl buffer pH 7.5, 8.3mM MgCl<sub>2</sub>, 1.7mM EGTA, 0.05% (w/v) bovine serum albumin for 10-30 minutes. The enzyme concentration was adjusted so that no more than 20% hydrolysis of the substrate occurred in control wells without compound, during the incubation. For PDE3 and PDE4B assay [5',8-<sup>3</sup>H]Adenosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech, code TRK.559) was added to give 0.05uCi per well and ~10nM final concentration. For PDE5 assay [8-<sup>3</sup>H]Guanosine 3',5'-cyclic phosphate (Amersham Pharmacia Biotech, code TRK.392) was added to give 0.05uCi per well and ~36nM final concentration. Plates were mixed on an orbital shaker for 5 minutes and incubated at ambient temperature for 1 hour. Phosphodiesterase SPA beads (Amersham Pharmacia Biotech, code RPNQ 0150) were added (~1mg per well) to terminate the assay. Plates were sealed and shaken and allowed to stand at ambient temperature for 1 hour to allow the beads to settle. Bound radioactive product was measured using a WALLAC TRILUX 1450 Microbeta scintillation counter. For inhibition curves, 10 concentrations (1.5nM - 30uM) of each compound were assayed. Curves were analysed using ActivityBase and XLfit (ID Businesss Solutions Limited) Results were expressed as pIC<sub>50</sub> values.

Biological Data obtained for some of the Examples (PDE4B inhibitory activity) is as follows:

| Example | PDE4B pIC <sub>50</sub> |
|---------|-------------------------|
| 2       | 7.99                    |
| 3       | 7.97                    |
| 11      | 7.41                    |
| 21      | 8.33                    |
| 22      | 7.85                    |
| 32      | 7.75                    |

25

*Emesis:* Many known PDE4 inhibitors cause emesis and/or nausea to greater or lesser extents (e.g. see Z. Huang et al., *Current Opinion in Chemical Biology*, 2001, 5: 432-438, see especially pages 433-434 and refs cited therein). Therefore, it would be preferable but not essential that a PDE4 inhibitory compound of the invention causes only limited or manageable emetic side-effects. Emetic side-effects can for example be measured by the emetogenic potential of the compound when administered to ferrets; for example one can measure the time to onset, extent, frequency and/or duration of vomiting and/or writhing in ferrets after oral or parenteral administration of the compound. See for example A. Robichaud et al., "Emesis induced by inhibitors of [PDE IV] in the ferret", *Neuropharmacology*, 1999, 38, 289-297, erratum *Neuropharmacology*, 2001, 40, 465-465.

35

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

## EXAMPLES

The various aspects of the invention will now be described by reference to the following examples. These examples are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In this section, "Intermediates" represent syntheses of intermediate compounds intended for use in the synthesis of the "Examples".

### Abbreviations used herein:

|                    |   |
|--------------------|---|
| DCM                | dichloromethane   |
| EtOAc              | ethyl acetate   |
| Et <sub>2</sub> O  | diethyl ether   |
| DMF                | dimethyl formamide  |
| MeOH               | methanol  |
| HPLC               | high pressure liquid chromatography                                       |
| SPE                | solid phase extraction  |
| NMR                | nuclear magnetic resonance  |
| LCMS               | liquid chromatography/mass spectroscopy                                   |
| TLC                | thin layer chromatography   |
| BEMP               | 2-t-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphazine |
| EDC                | 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride               |
| HOBT               | hydroxybenzotriazole  |
| HBTU               | O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate    |
| DIPEA              | diisopropylethyl amine  |
| THF                | Tetrahydrofuran   |
| Lawesson's reagent | 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide      |

### Machine Methods used herein:

#### LCMS (liquid chromatography/mass spectroscopy)

Waters ZQ mass spectrometer operating in positive ion electrospray mode, mass range 100-1000 amu.  
UV wavelength : 215-330nm  
Column : 3.3cm x 4.6mm ID, 3µm ABZ+PLUS

Flow Rate : 3ml/min

Injection Volume : 5µl

Solvent A : 95% acetonitrile + 0.05% formic acid

Solvent B : 0.1% formic acid + 10mMolar ammonium acetate

5 Gradient : 0% A/0.7min, 0-100% A/3.5min, 100% A/1.1min, 100-0% A/0.2min

#### Mass directed autoprep HPLC

The prep column used was a Supelcosil ABZplus (10cm x 2.12cm)

UV wavelength : 200-320nm

10 Flow : 20ml/min

Injection Volume: 1ml

Solvent A : 0.1% formic acid

Solvent B : 95% acetonitrile + 5% formic acid

Gradient : 100% A/1min, 100-80% A/9min, 80-1% A/3.5min, 1% A/1.4min, 1-

15 100%A/0.1min

#### Intermediates and Examples

20 All reagents not detailed in the text below are commercially available from established suppliers such as Sigma-Aldrich.

#### Table of Intermediates

| Inter-<br>mediate<br>Number | Name  |
|-----------------------------|---|
| 1                           | Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                     |
| 2                           | Ethyl 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                             |
| 3                           | Ethyl 1-methyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                    |
| 4                           | Ethyl 1-benzyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                    |
| 5                           | Ethyl 4-chloro-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                    |
| 6                           | 1-Acetyl-4-aminopiperidine  |
| 7                           | 1-Methyl-4-aminopiperidine  |
| 8                           | 4-Aminotetrahydropyran  |
| 8A                          | Tetrahydro-2H-pyran-4-amine hydrochloride =<br>4-Aminotetrahydropyran hydrochloride |
| 9                           | (R)-(+)-3-Amino tetrahydrofuran 4-toluene sulphonate                                |
| 10                          | (S)-(-)-3-Amino tetrahydrofuran 4-toluene sulphonate                                |
| 11                          | Tetrahydro-2H-thiopyran-4-amine   |
| 12                          | Tetrahydro-3-thiopheneamine   |
| 13                          | Tetrahydro-3-thiopheneamine 1,1-dioxide hydrochloride                               |
| 14                          | Tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride                           |

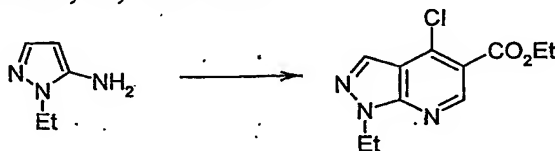
|    |   |
|----|---|
| 15 | 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid   |
| 16 | 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl chloride   |
| 17 | N-Benzyl-4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide  |
| 18 | 4-Chloro-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                                |
| 19 | 4-Chloro-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                              |
| 20 | 4-Chloro-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                                   |
| 21 | 4-Chloro-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridine                                   |
| 22 | 4-Chloro-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                          |
| 23 | 4-Chloro-1-ethyl-N-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide  |
| 24 | 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide   |
| 25 | Ethyl 4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate  |
| 26 | 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid  |
| 27 | 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carbonyl chloride  |
| 28 | N-Benzyl-4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                                       |
| 29 | 4-Chloro-1-methyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                             |
| 30 | 4-Chloro-1-methyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                               |
| 31 | 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide  |
| 32 | Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                  |
| 33 | 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid                    |
| 34 | Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                 |
| 35 | Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                 |
| 36 | Ethyl 1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate              |
| 37 | Ethyl 1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                      |
| 38 | Ethyl 4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                               |
| 39 | Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate         |
| 40 | Ethyl 4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate |
| 41 | 1-Ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid                   |
| 42 | Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid             |
| 43 | 1-Ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid                |



|    |   |
|----|---|
| 44 | 1-Ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid                      |
| 45 | 4-(Cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid                               |
| 46 | 4-[(1,1-Dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid         |
| 47 | 4-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid |

**Intermediate 1: Ethyl 4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**

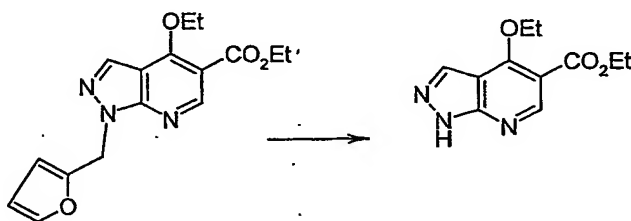
Prepared from commercially available 5-amino-1-ethyl pyrazole as described by G. Yu et. al. in *J. Med. Chem.*, 2001, 44, 1025-1027:



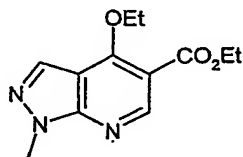
**Intermediate 2: Ethyl 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**

Prepared by oxidative cleavage ( $\text{SeO}_2$ ) of 1-furanmethyl derivative, as described by T.

- 10 M. Bare et. al. In *J. Med. Chem.*, 1989, 32, 2561-2573, (further referenced to Zuleski, F. R., Kirkland, K. R., Melgar, M. D.; Malbica, *J. Drug. Metab. Dispos.*, 1985, 13, 139)



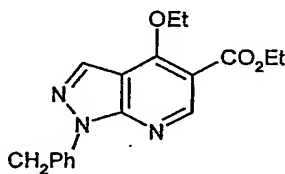
- 15 **Intermediate 3: Ethyl 1-methyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**



- 20 A mixture of Intermediate 2 (0.47g) and anhydrous potassium carbonate (0.83g) (previously dried by heating at 100°C) in anhydrous dimethylformamide (DMF) (4ml) was treated with iodomethane (0.26ml) and stirred vigorously for 3h. The mixture was then filtered and the filtrate concentrated in vacuo to afford a residual oil, which was partitioned between dichloromethane (DCM) (25ml) and water (25ml). The layers were separated and the aqueous phase was extracted with further DCM (2x25ml). The

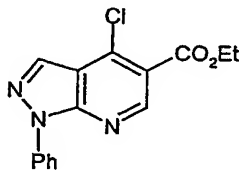
combined organic extracts were dried over anhydrous sodium sulphate and evaporated to an orange solid which was applied to an SPE cartridge (silica, 20g). The cartridge was eluted sequentially with EtOAc : petrol (1:4, 1:2 and 1:1), then chloroform : methanol (49:1, 19:1 and 9:1). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 3 (0.165g). LCMS showed  $MH^+ = 250$ ;  $T_{RET} = 2.59$  min.

**Intermediate 4: Ethyl 1-benzyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**



A mixture of Intermediate 2 (0.47g) and anhydrous potassium carbonate (0.83g) (previously dried by heating at 100°C) in anhydrous DMF (4ml) was treated with benzyl bromide (0.72g) then stirred vigorously and heated at 55°C for 4.5h. The mixture was allowed to cool, then filtered and the filtrate concentrated in vacuo to afford a residual oil, which was partitioned between DCM (25ml) and water (25ml). The layers were separated and the aqueous phase was extracted with further DCM (2x25ml). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated to a yellow oily solid which was dissolved in DCM and applied to an SPE cartridge (silica, 20g). The cartridge was eluted with a gradient of EtOAc : petrol (1:44, 1:2 and 1:1) then chloroform : methanol (49:1, 19:1 and 9:1). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 4 (0.33g). LCMS showed  $MH^+ = 326$ ;  $T_{RET} = 3.24$  min.

**Intermediate 5: Ethyl 4-chloro-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**

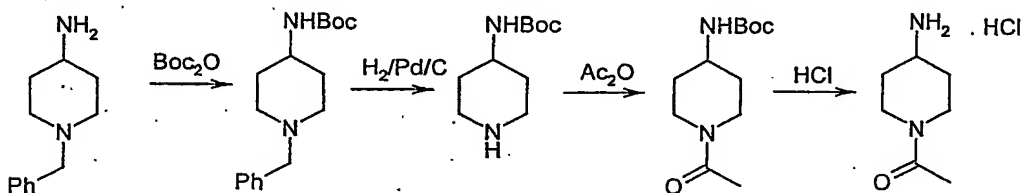


A mixture of 5-amino-1-phenyl pyrazole (2.0g) and diethylethoxymethylene malonate (2.54ml) was heated under Dean Stark conditions at 120°C for 16h. The solution was cooled, phosphorus oxychloride (16ml) was then added and the mixture heated under reflux for a further 20h. Excess phosphorus oxychloride was removed in vacuo and the residue partitioned between diethyl ether and water, proceeding with extreme caution on addition of water. The ethereal layer was washed with further water, then dried over magnesium sulphate and concentrated in vacuo to afford ethyl 4-ethoxy-1-phenyl-1H-

pyrazolo[3,4-b]pyridine-5-carboxylate (2.09g). LCMS showed  $MH^+ = 302$ ;  $T_{RET} = 3.80$  min.

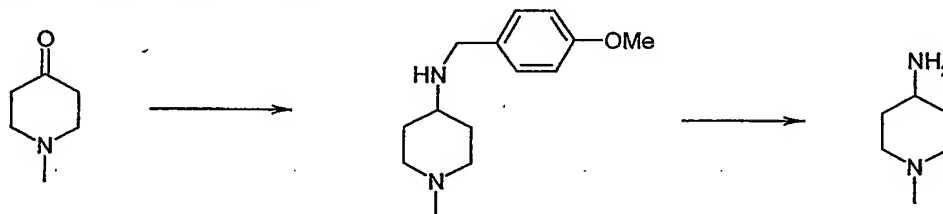
**Intermediate 6: 1-Acetyl-4-aminopiperidine**

- 5 Prepared from commercially available N1-benzyl-4-aminopiperidine as described by Yamada *et. al.* In WO 00/42011:



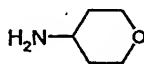
10 **Intermediate 7: 1-Methyl-4-aminopiperidine**

Prepared from commercially available N-methyl-4-piperidone as described by C. M. Andersson *et. al.* in WO01/66521:

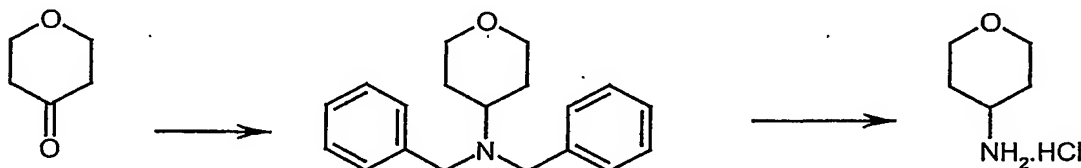


15 **Intermediate 8: 4-Aminotetrahydropyran**

Commercially available from Combi-Blocks Inc., 7949 Silverton Avenue, Suite 915, San Diego, CA 92126 (CAS 38041-19-9)



20 **Intermediate 8A: Tetrahydro-2H-pyran-4-amine hydrochloride = 4-Aminotetrahydropyran hydrochloride**



25 **Step1: N,N-dibenzyltetrahydro-2H-pyran-4-amine**

Dibenzylamine (34.5g) and acetic acid (6.7ml) were added to a stirred solution of tetrahydro-4H-pyran-4-one (16.4g, commercially available from e.g. Aldrich) in dichloromethane (260ml) at 0 °C to 5 °C. After 2.5h at 0 °C to 5 °C, sodium triacetoxyborohydride (38.9g) was added portionwise, and the mixture was allowed to warm to room temperature. After stirring at room temperature overnight, the reaction

30

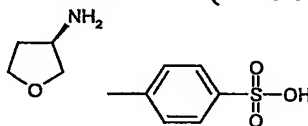
mixture was washed successively with 2M-sodium hydroxide (200ml and 50ml), water (2 x 50ml) and brine (50ml), then dried and evaporated to give a yellow oil (45g). This oil was stirred with methanol (50ml) at 4 °C for 30min to give the product as a white solid (21.5g). LCMS showed  $MH^+ = 282$ ;  $T_{RET} = 1.98$  min.

5

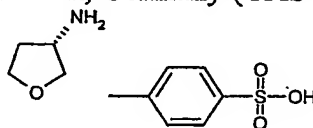
**Step 2: Tetrahydro-2H-pyran-4-amine hydrochloride**

*N,N*-dibenzyltetrahydro-2H-pyran-4-amine (20.5g) was dissolved in ethanol (210ml) and hydrogenated over 10% palladium on carbon catalyst (4g) at 100 psi for 72h at room temperature. The reaction mixture was filtered and the filtrate was adjusted to pH 1 with 2M-hydrogen chloride in diethyl ether. Evaporation of solvents gave a solid which was triturated with diethyl ether to give the product as a white solid (9.23g).  $^1H$  NMR (400MHz in  $d_6$ -DMSO, 27°C,  $\delta$ ppm) 8.24 (br. s, 3H), 3.86 (dd, 12, 4Hz, 2H), 3.31 (dt, 2, 12Hz, 2H), 3.20 (m, 1H), 1.84 (m, 2H), 1.55 (dq, 4, 12Hz, 2H).

15 **Intermediate 9: (R)-(+)-3-Amino tetrahydrofuran 4-toluenesulphonate**  
Commercially available from Fluka Chemie AG (CAS 111769-27-8)

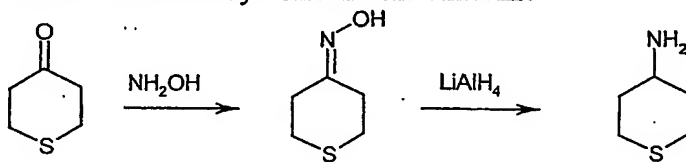


20 **Intermediate 10: (S)-(-)-3-Amino tetrahydrofuran 4-toluenesulphonate**  
Commercially available from E. Merck, Germany (CAS 104530-80-5)



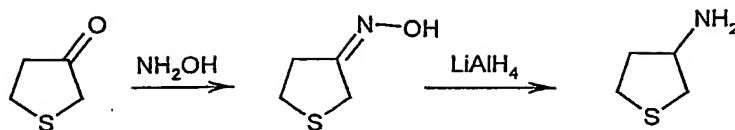
**Intermediate 11: Tetrahydro-2H-thiopyran-4-amine**

25 Prepared from commercially available tetrahydrothiopyran-4-one as described by Subramanian et. al., *J. Org. Chem.*, 1981, 46, 4376-4383. Subsequent preparation of the hydrochloride salt can be achieved by conventional means.



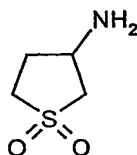
**Intermediate 12: Tetrahydro-3-thiopheneamine**

30 Prepared in an analogous manner to Intermediate 11 from commercially available tetrahydrothiophene-4-one. The oxime formation is described by Grigg et.al., *Tetrahedron*, 1991, 47, 4477-4494 and the oxime reduction by Unterhalt et. al., *Arch. Pharm.*, 1990, 317-318.



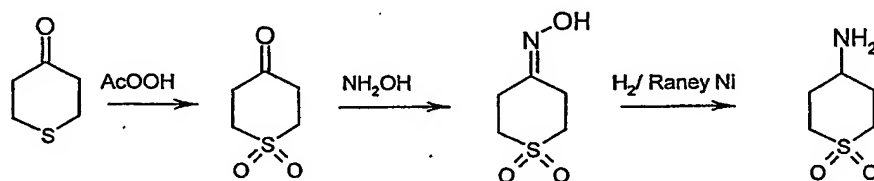
**Intermediate 13: Tetrahydro-3-thiopheneamine 1,1-dioxide hydrochloride**

- 5 Commercially available from Sigma Aldrich Library of Rare Chemicals (SALOR) (CAS-6338-70-1). Preparation of the hydrochloride salt of the amine can be achieved by conventional means.

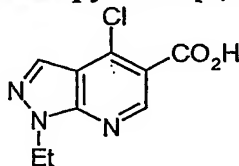


10 **Intermediate 14: Tetrahydro-2H-thiopyran-4-amine-1,1-dioxide hydrochloride**

Prepared in an analogous manner to Intermediate 11 from commercially available tetrahydrothiophene-4-one. Oxidation to 1,1-dioxo-tetrahydro-1 $\lambda^6$ -thiopyran-4-one is described by Rule et. al., in *J. Org. Chem.*, 1995, 60, 1665-1673. Oxime formation is described by Truce et.al., in *J. Org. Chem.*, 1957, 617, 620 and oxime reduction by Barkenbus et. al., *J. Am. Chem. Soc.*, 1955, 77, 3866. Subsequent preparation of the hydrochloride salt of the amine can be achieved by conventional means.



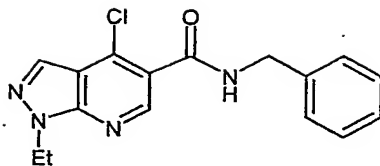
20 **Intermediate 15: 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid**



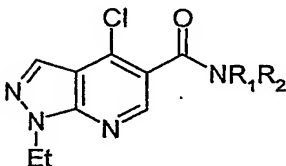
- A solution of Intermediate 1 (3.5g) in dioxane (28ml) was treated with potassium hydroxide (6.3g) as a solution in water (20ml). The mixture was stirred for 2h, then concentrated in vacuo, acidified to pH 3 with 2M aqueous hydrochloric acid and  
 25 extracted with ethyl acetate. The layers were separated, the organic layer dried over sodium sulphate, then concentrated in vacuo to afford Intermediate 15 as a white solid (2.4g). LCMS showed  $MH^+ = 226$ ;  $T_{RET} = 2.62$ min.

**Intermediate 17: N-Benzyl-4-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide**

30



That is, Intermediate 17 is:

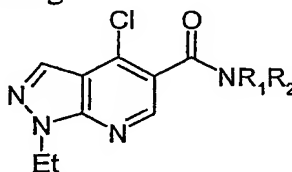


wherein  $NR_1R_2 =$

Intermediate 15 (3.5g) was dried over phosphorus pentoxide for 1h, then treated with thionyl chloride (47g). The mixture was stirred and heated at 75°C for 1.3h. Excess thionyl chloride was removed in vacuo and the residual oil azeotroped with dichloromethane (DCM) to afford **Intermediate 16**, the acid chloride derivative of Intermediate 15, as a white solid (3.3g).

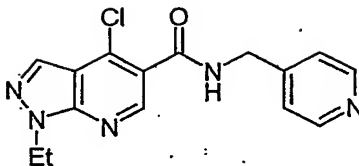
Intermediate 16 (0.473g) was dissolved in tetrahydrofuran (THF) (4ml) and treated with N,N-diisopropylethylamine (DIPEA) (0.509ml), then with benzylamine (0.209g) and the mixture stirred under nitrogen for 0.5h. The mixture was concentrated in vacuo, then partitioned between dichloromethane and water. The layers were separated and the organics concentrated in vacuo to afford **Intermediate 17** (0.574g). LCMS showed  $MH^+ = 315$ ;  $T_{RET} = 2.90$ min.

Similarly prepared were the following:



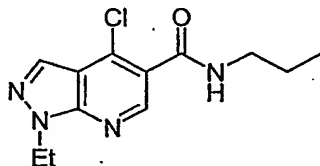
|                        | NR <sub>1</sub> R <sub>2</sub> | Amine reagent        | MH <sup>+</sup><br>ion | T <sub>RET</sub><br>(min) |
|------------------------|--------------------------------|----------------------|------------------------|---------------------------|
| <b>Intermediate 18</b> |                                | 2-Ethyl-N-butylamine | 309                    | 3.07                      |
| <b>Intermediate 19</b> |                                | 4-Fluoroaniline      | 319                    | 3.08                      |
| <b>Intermediate 20</b> |                                | Cyclopentylamine     | 293                    | 2.76                      |
| <b>Intermediate 21</b> |                                | Pyrrolidine          | 279                    | 2.46                      |

**Intermediate 22:** 4-Chloro-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



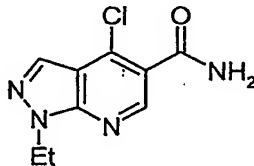
Acid chloride Intermediate 16 was synthesised from Intermediate 15 using the method shown above for Intermediate 17. Intermediate 16 (0.473g) was dissolved in THF (4ml) and treated with diisopropylethylamine (DIPEA) (0.509ml), then with 4-(aminomethyl)pyridine (0.211g) and the mixture stirred under nitrogen for 0.5h. The mixture was concentrated in vacuo, then partitioned between DCM and water. The layers were separated and the organics concentrated in vacuo, then applied to an SPE cartridge (silica, 10g) which was eluted with a gradient of cyclohexane : EtOAc (2:1 increasing stepwise up to 0:1), followed by MeOH : EtOAc (5:95, then 10:90). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 22 (0.086g). LCMS showed  $MH^+ = 316$ ;  $T_{RET} = 1.84$ min.

**Intermediate 23:** 4-Chloro-1-ethyl-N-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



Acid chloride Intermediate 16 was synthesised from Intermediate 15 using the method shown above for Intermediate 17. Intermediate 16 (0.473g) was dissolved in THF (4ml) and treated with DIPEA (0.509ml), then with propyl amine (0.115g) and the mixture stirred under nitrogen for 0.5h. A further portion of propyl amine (0.023g) was then added and stirring continued for 18h. The mixture was concentrated in vacuo, then partitioned between DCM and water. The layers were separated and the organics concentrated in vacuo to afford Intermediate 23 (0.405g). LCMS showed  $MH^+ = 267$ ;  $T_{RET} = 2.54$ min.

**Intermediate 24:** 4-Chloro-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

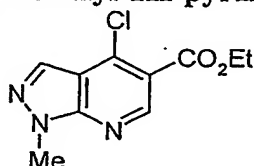


Acid chloride Intermediate 16 was synthesised from Intermediate 15 using the method shown above for Intermediate 17. Intermediate 16 (0.30g) was dissolved in THF (3ml) and treated with a 0.5M solution of ammonia in dioxane (4.92ml). The mixture was stirred under nitrogen for 18h. A further portion of 0.5M ammonia in dioxane (4.92ml)

was added and stirring continued for 72h. The mixture was concentrated in vacuo and the residue partitioned between DCM and 2M sodium hydroxide solution. The layers were separated and the organics concentrated to afford Intermediate 24 (0.278g). LCMS showed  $MH^+ = 225$ ;  $T_{RET} = 2.10\text{min}$ .

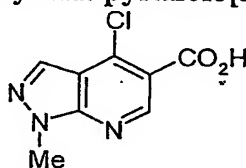
5

**Intermediate 25: Ethyl 4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**



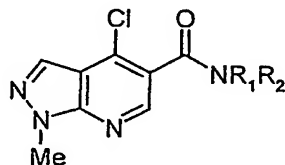
A mixture of 5-amino-1-methyl pyrazole (4.0g) and diethylethoxymethylene malonate (9.16ml) was heated at  $150^\circ\text{C}$  under Dean Stark conditions for 5h. Phosphorous oxychloride (55ml) was carefully added to the mixture and the resulting solution heated at  $130^\circ\text{C}$  under reflux for 18h. The mixture was concentrated in vacuo, then the residual oil cooled in an ice bath and treated carefully with water (100ml)(caution: exotherm). The resulting mixture was extracted with DCM (3x100ml) and the combined organic extracts were dried over anhydrous sodium sulphate and concentrated in vacuo. The residual solid was purified by Biotage chromatography (silica, 90g), eluting with  $\text{Et}_2\text{O}$  : petrol (1:3). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 25 (4.82g). LCMS showed  $MH^+ = 240$ ;  $T_{RET} = 2.98\text{min}$ .

**Intermediate 26: 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid**



A solution of Intermediate 25 (4.0g) in dioxane (30ml) was treated with potassium hydroxide (7.54g) as a solution in water (20ml). The mixture was stirred for 16h, then diluted with water (150ml) and acidified to pH 3 with 5M aqueous hydrochloric acid. The mixture was stirred in an ice bath for 15min, then collected by filtration, washed with ice-cold water and dried in vacuo over phosphorous pentoxide to afford Intermediate 26 as a white solid (2.83g). LCMS showed  $MH^+ = 212$ ;  $T_{RET} = 2.26\text{min}$ .

**Intermediate 28: N-Benzyl-4-chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide**



Intermediate 28  $NR_1R_2 = \text{HN}-\text{CH}_2-\text{C}_6\text{H}_5$

30



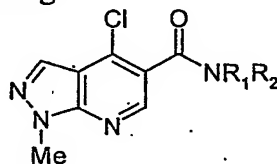
Intermediate 26 (2.5g) (previously dried over phosphorus pentoxide) was treated with thionyl chloride (25ml) and the mixture heated under reflux for 1h. Excess thionyl chloride was removed in vacuo to afford **Intermediate 27**, the acid chloride derivative of Intermediate 26, as a white solid (2.7g).

5

Intermediate 27 (0.68g) was dissolved in THF (10ml) and treated with DIPEA (0.77ml), then with benzyl amine (0.339g) and the mixture stirred under nitrogen for 3h. The mixture was concentrated in vacuo, then partitioned between DCM (20ml) and water (10ml). The layers were separated and the organics concentrated in vacuo to afford **Intermediate 28** (0.90g). LCMS showed  $MH^+ = 301$ ;  $T_{RET} = 2.72$ min.

10

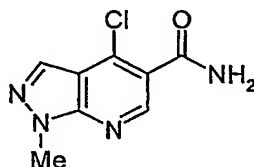
Similarly prepared were the following:



|                        | NR <sub>1</sub> R <sub>2</sub> | Amine reagent        | $MH^+$ ion | $T_{RET}$ (min) |
|------------------------|--------------------------------|----------------------|------------|-----------------|
| <b>Intermediate 29</b> |                                | 4-Fluoroaniline      | 305        | 2.91            |
| <b>Intermediate 30</b> |                                | 2-Ethyl-N-butylamine | 295        | 2.97            |

15

**Intermediate 31: 4-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide**

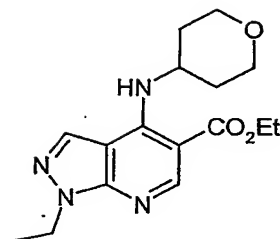


20

Acid chloride Intermediate 27 was synthesised from Intermediate 26 using the method shown above for Intermediate 28. Intermediate 27 (0.68g) was then treated with a 0.5M solution of ammonia in dioxane (17.7ml). Diisopropylethylamine (0.51ml) was then added and the mixture stirred for 21h. The mixture was then partitioned between DCM (100ml) and water (30ml). An insoluble solid was removed by filtration, washed with water (20ml) and dried in vacuo over phosphorous pentoxide to afford Intermediate 31 (0.544g). LCMS showed  $MH^+ = 211$ ;  $T_{RET} = 1.84$ min.

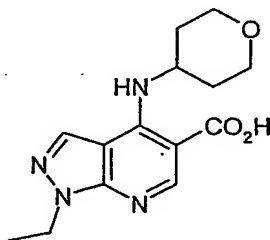
25

**Intermediate 32 (= Example 3): Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**



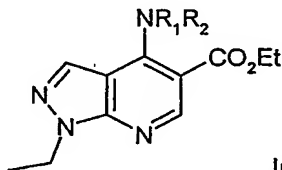
Intermediate 1 (0.20g) and triethylamine (0.55ml) were suspended in ethanol (8ml) and 4-aminotetrahydropyran (0.088g) was added. The mixture was stirred under nitrogen, heated at 80°C for 16h, then concentrated in vacuo. The residue was partitioned between DCM and water. The layers were separated and the organic layer was loaded directly onto an SPE cartridge (silica, 5g) which was eluted sequentially with; (i) DCM, (ii) DCM : Et<sub>2</sub>O (2:1), (iii) DCM : Et<sub>2</sub>O (1:1), (iv) Et<sub>2</sub>O and (v) EtOAc. Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 32 (0.21g). LCMS showed MH<sup>+</sup> = 319; T<sub>RET</sub> = 2.93min.

**Intermediate 33:** 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid



A solution of Intermediate 32 (0.21g) in ethanol : water (95:5, 10ml) was treated with sodium hydroxide (0.12g). The mixture was heated at 50°C for 8h, then concentrated in vacuo, dissolved in water and acidified to pH 4 with acetic acid. The resultant white solid was removed by filtration and dried under vacuum to afford Intermediate 33 as an off-white solid (0.156g). LCMS showed MH<sup>+</sup> = 291; T<sub>RET</sub> = 2.11min.

**Intermediate 34:** Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

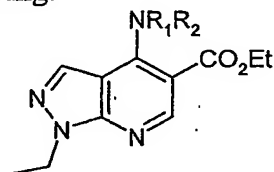


Intermediate 34 NR<sub>1</sub>R<sub>2</sub> =

Intermediate 1 (0.05g) and (S)-(-)-3-aminotetrahydrofuran 4-toluenesulphonate (0.052g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature,

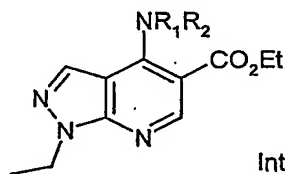
ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:16 then, 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 34 (0.052g). LCMS showed  $MH^+ = 305$ ;  $T_{RET} = 2.70$ min.

Similarly prepared were the following:



|                 | $NR_1R_2$ | Amine Reagent                                      | $MH^+$<br>ion | $T_{RET}(min)$ |
|-----------------|-----------|--|---------------|----------------|
| Intermediate 35 |           | (R)-(+)-3-Aminotetrahydrofuran 4-toluenesulphonate | 305           | 2.73           |
| Intermediate 36 |           | Intermediate 11                                    | 335           | 3.21           |
| Intermediate 37 |           | Intermediate 12                                    | 321           | 3.10           |
| Intermediate 38 |           | Cyclopropylamine                                   | 275           | 2.98           |

**Intermediate 39:** Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

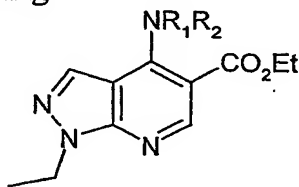


Intermediate 39  $NR_1R_2 =$

Intermediate 1 (0.05g) and Intermediate 13 (0.027g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of

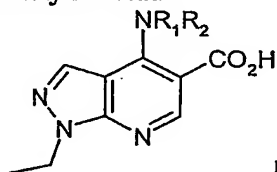
EtOAc : cyclohexane; (1:8 then 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Intermediate 39 (0.045g) as a mixture of enantiomers. LCMS showed  $MH^+ = 353$ ;  $T_{RET} = 2.60$ min.

5 Similarly prepared was the following:



|                    | $NR_1R_2$ | Amine Reagent   | $MH^+$<br>ion | $T_{RET}(\text{min})$ |
|--------------------|-----------|-----------------|---------------|-----------------------|
| Intermediate<br>40 |           | Intermediate 14 | 367           | 2.64                  |

10 **Intermediate 41:** 1-Ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

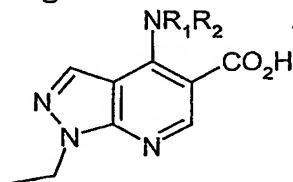


Intermediate 41  $NR_1R_2 =$


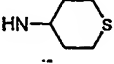

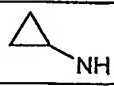
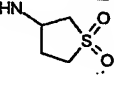
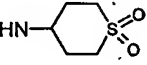
A solution of Intermediate 34 (0.037g) in ethanol : water (95:5, 3ml) was treated with sodium hydroxide (0.019g). The mixture was heated at 50°C for 16h, then concentrated in vacuo. The residue was dissolved in water (1.5ml) and acidified to pH 4 with acetic acid.  
 15 The resultant white solid precipitate was removed by filtration and dried under vacuum. The filtrate was extracted with ethyl acetate and the organic layer collected and concentrated in vacuo to afford a further portion of white solid. The two solids were combined to afford Intermediate 41 (0.033g). LCMS showed  $MH^+ = 277$ ;  $T_{RET} = 2.05$  min.

20

Similarly prepared were the following:



|  | $NR_1R_2$ | Starting material | $MH^+$<br>ion | $T_{RET}(\text{min})$ |
|--|-----------|-------------------|---------------|-----------------------|
|--|-----------|-------------------|---------------|-----------------------|

|                            |   |                        |     |      |
|----------------------------|---|------------------------|-----|------|
| <b>Intermediate<br/>42</b> |  | <b>Intermediate 35</b> | 277 | 2.05 |
| <b>Intermediate<br/>43</b> |  | <b>Intermediate 36</b> | 307 | 2.40 |
| <b>Intermediate<br/>44</b> |  | <b>Intermediate 37</b> | 293 | 2.59 |
| <b>Intermediate<br/>45</b> |  | <b>Intermediate 38</b> | 247 | 2.24 |
| <b>Intermediate<br/>46</b> |  | <b>Intermediate 39</b> | 325 | 2.05 |
| <b>Intermediate<br/>47</b> |  | <b>Intermediate 40</b> | 339 | 2.05 |

### Table of Examples

| Example<br>Number | Name   |
|-------------------|--|
| 1                 | Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                  |
| 2                 | Ethyl 4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                   |
| 3                 | Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate     |
| 4                 | Ethyl 4-[(1-methylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate     |
| 5                 | Ethyl 4-[(1-acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate     |
| 6                 | Ethyl 4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                 |
| 7                 | Ethyl 1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate    |
| 8                 | Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate    |
| 9                 | Ethyl 1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate    |
| 10                | Ethyl 1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate |
| 11                | Ethyl 1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-                    |

|    |   |
|----|---|
|    | carboxylate   |
| 12 | Ethyl 4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                               |
| 13 | Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate         |
| 14 | Ethyl 4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate |
| 15 | Ethyl 4-(cyclopentylamino)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                              |
| 16 | Ethyl 1-phenyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                 |
| 17 | Ethyl 4-(cyclopentylamino)-1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                              |
| 18 | Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                 |
| 19 | Ethyl 4-(cyclopentylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                                       |
| 20 | Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate                          |
| 21 | N-Benzyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide               |
| 22 | 1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide     |
| 23 | N-Cyclopentyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                       |
| 24 | 4-(Cyclohexylamino)-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                        |
| 25 | N-Cyclopentyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide          |
| 26 | N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide          |
| 27 | 4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide          |
| 28 | N-Cyclopentyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridin-4-amine                       |
| 29 | N-Cyclohexyl-1-ethyl-5-(pyrrolidin-1-ylcarbonyl)-1H-pyrazolo[3,4-b]pyridin-4-amine                        |
| 30 | 1-Ethyl-5-(pyrrolidin-1-ylcarbonyl)-N-tetrahydro-2H-pyran-4-yl-1H-pyrazolo[3,4-b]pyridin-4-amine          |
| 31 | 4-(Cyclopentylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide              |
| 32 | 4-(Cyclohexylamino)-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide               |
| 33 | 1-Ethyl-N-(pyridin-4-ylmethyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide |

|    |   |
|----|---|
| 34 | 4-(Cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                                 |
| 35 | 4-(Cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                                  |
| 36 | 1-Ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                    |
| 37 | 1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                    |
| 38 | 4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                    |
| 39 | N-Benzyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                        |
| 40 | N-Benzyl-4-(cyclohexylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                         |
| 41 | 4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide           |
| 42 | 4-(Cyclopentylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                |
| 43 | 4-(Cyclohexylamino)-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                 |
| 44 | 1-Ethyl-N-(2-ethylbutyl)-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide   |
| 45 | 1-Ethyl-N-(2-ethylbutyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide   |
| 46 | 4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(2-ethylbutyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide   |
| 47 | 4-(Cyclopentylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide              |
| 48 | 4-(Cyclohexylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide               |
| 49 | 1-Ethyl-N-(4-fluorophenyl)-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide |
| 50 | 4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide |
| 51 | 4-(Cyclopentylamino)-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                      |
| 52 | 4-(Cyclohexylamino)-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                       |
| 53 | 1-Ethyl-N-n-propyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide         |
| 54 | 1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide         |
| 55 | 4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-n-propyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide         |

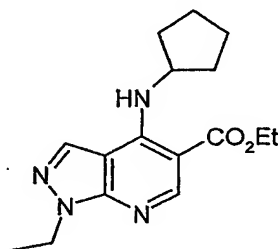
|    |   |
|----|---|
|    | b]pyridine-5-carboxamide  |
| 56 | N-Benzyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide               |
| 57 | 4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide |
| 58 | 1-Ethyl-4-[(1-methylpiperidin-4-yl)amino]-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide |
| 59 | N-Cyclopentyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide          |
| 60 | 4-[(1-Acetylpiperidin-4-yl)amino]-N-cyclopentyl-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide          |
| 61 | N-Benzyl-4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                           |
| 62 | N-Benzyl-4-(cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                            |
| 63 | N-Benzyl-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide              |
| 64 | 4-(Cyclopentylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                   |
| 65 | 4-(Cyclohexylamino)-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                    |
| 66 | N-(2-Ethylbutyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide      |
| 67 | 4-(Cyclopentylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                 |
| 68 | 4-(Cyclohexylamino)-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                  |
| 69 | N-(4-Fluorophenyl)-1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide    |
| 70 | 4-(Cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                                    |
| 71 | 4-(Cyclohexylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                                     |
| 72 | 1-Methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                       |
| 73 | N-Benzyl-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide              |
| 74 | 4-[(1-Acetylpiperidin-4-yl)amino]-N-benzyl-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide              |
| 75 | N-(2-Ethylbutyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide      |
| 76 | 4-[(1-Acetylpiperidin-4-yl)amino]-N-(2-ethylbutyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide      |



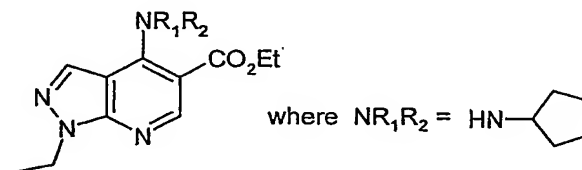
|    |  |
|----|--|
| 77 | N-(4-Fluorophenyl)-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide       |
| 78 | 4-[(1-Acetylpiperidin-4-yl)amino]-N-(4-fluorophenyl)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide       |
| 79 | 1-Methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                          |
| 80 | 4-[(1-Acetylpiperidin-4-yl)amino]-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                          |
| 81 | 1-Ethyl-N-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                  |
| 82 | 1-Ethyl-N,N-dimethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide              |
| 83 | 1-Ethyl-N-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                   |
| 84 | 1-Ethyl-N-isopropyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide               |
| 85 | N-Benzyl-1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                 |
| 86 | N-Benzyl-1-ethyl-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                 |
| 87 | N-Benzyl-1-ethyl-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                      |
| 88 | N-Benzyl-4-(cyclopropylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                               |
| 89 | N-Benzyl-4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide         |
| 90 | N-Benzyl-4-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide |
| 91 | N-Benzyl-1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide              |
| 92 | 1-Ethyl-N-(4-fluorophenyl)-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide       |
| 93 | 1-Ethyl-N-(4-fluorophenyl)-4-[(3R)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide       |
| 94 | 1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide    |
| 95 | 1-Ethyl-N-(4-fluorophenyl)-4-(tetrahydrothien-3-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide            |
| 96 | 4-(Cyclopropylamino)-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide                     |
| 97 | 4-[(1,1-Dioxidotetrahydrothien-3-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-                                    |

|    |  |
|----|--|
|    | pyrazolo[3,4-b]pyridine-5-carboxamide  |
| 98 | 4-[(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)amino]-1-ethyl-N-(4-fluorophenyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide |

**Example 1:** Ethyl 4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



That is, Example 1 is

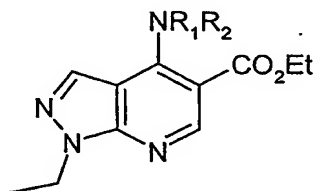


5

Intermediate 1 (0.051g) and cyclopentyl amine (0.019g) were suspended in ethanol (2ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated, at 80°C for 16h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between dichloromethane (DCM) and water. The layers were separated and the organic layer was loaded directly onto an solid phase extraction (SPE) cartridge (silica, 5g) which was eluted sequentially with; (i) DCM, (ii) DCM : Et<sub>2</sub>O (2:1), (iii) DCM : Et<sub>2</sub>O (1:1), (iv) Et<sub>2</sub>O, (v) EtOAc, (vi) MeOH. Fractions containing desired material were combined and concentrated in vacuo to afford Example 1 (0.074g). LCMS showed  $MH^+ = 303$ ;  $T_{RET} = 3.45\text{min}$ .



15

Similarly prepared were the following:

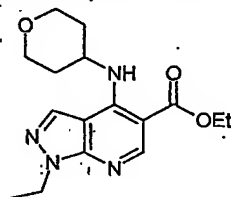


20

|           | $NR_1R_2$ | Amine reagent    | $MH^+$ ion | $T_{RET}(\text{min})$ |
|-----------|-----------|------------------|------------|-----------------------|
| Example 2 |           | Cyclohexyl amine | 317        | 3.65                  |
| Example 3 |           | 4-Amino          | 319        | 2.93                  |

|                  |   |                 |     |      |
|------------------|---|-----------------|-----|------|
|                  |   | tetrahydropyran |     |      |
| <b>Example 4</b> |  | Intermediate 7  | 332 | 2.17 |
| <b>Example 5</b> |  | Intermediate 6  | 360 | 3.20 |

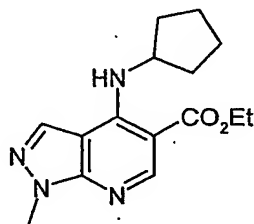
**Example 3 (=Intermediate 32):** Ethyl 1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



- 5 Instead of the method shown above (called Method A), the compound of Example 3 can also be made using the following method:

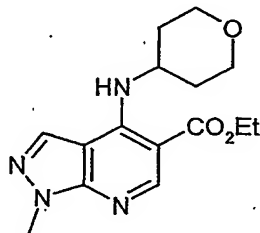
**Example 3, Method B:** Intermediate 1 (2.5g) was dissolved in acetonitrile (15ml). 4-Aminotetrahydropyran hydrochloride (1.1g) and N,N-diisopropylethylamine (9.4ml) were added and the mixture stirred under nitrogen at 85°C for 16h. A trace of starting material remained, so an additional portion of 4-aminotetrahydropyran hydrochloride (0.11g) was added and stirring continued at 85°C for a further 16h. The mixture was then concentrated in vacuo. The residue was partitioned between DCM and water. The layers were separated and the organic layer was washed with further water (2x20ml) then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was further purified by chromatography using Biotage (silica, 90g), eluting with cyclohexane : ethyl acetate to afford Example 21 (2.45g). LCMS showed MH<sup>+</sup> = 319; T<sub>RET</sub> = 2.90min.

20 **Example 6:** Ethyl 4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



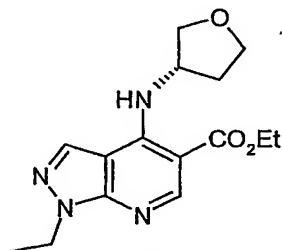
25 Intermediate 3 (0.045g) was placed in a Reactivial™ and treated with cyclopentyl amine (0.07ml). The mixture was heated at 90°C for 2h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was evaporated to a brown solid, which was purified by mass directed autoprep HPLC, to afford Example 6 as a white solid (0.008g). LCMS showed MH<sup>+</sup> = 289; T<sub>RET</sub> = 3.22 min.

**Example 7:** Ethyl 1-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

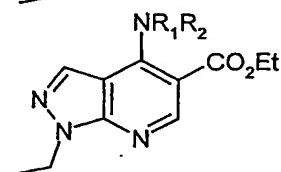


Intermediate 3 (0.035g) was placed in a Reactivial™ and treated with 4-amino tetrahydropyran (0.06ml). The mixture was heated at 90°C for 2h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated, then applied to a preparative TLC plate (silica, 20cm x 20cm x 1mm) which was eluted with ethyl acetate. The required band was removed from the plate and the silica washed with ethyl acetate (2 x 15ml). Concentration of the ethyl acetate solution *in vacuo* afforded Example 7 as a white solid (0.008g). LCMS showed  $MH^+ = 305$ ;  $T_{RET} = 2.67$  min.

**Example 8:** Ethyl 1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



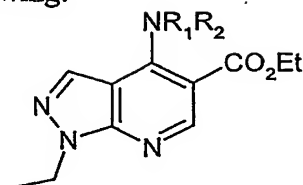
that is:



where  $NR_1R_2 =$

Intermediate 1 (0.05g) and (S)-(-)-3-aminotetrahydrofuran 4-toluene sulphonate (0.052g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:16 then, 1:8, 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated *in vacuo* to afford Example 8 (0.052g). LCMS showed  $MH^+ = 305$ ;  $T_{RET} = 2.70$ min.

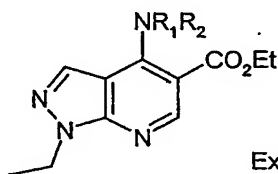
Similarly prepared were the following:



|   | NR <sub>1</sub> R <sub>2</sub> | Amine Reagent  | MH <sup>+</sup><br>ion | T <sub>RET</sub> (min) |
|---|--------------------------------|--|------------------------|------------------------|
| <b>Example 9</b>                              |                                | (R)-(+)-3-Aminotetrahydrofuran<br>4-toluene sulphonate | 305                    | 2.73                   |
| <b>Example 10</b><br>(mixture of enantiomers) |                                | Intermediate 11  | 335                    | 3.21                   |
| <b>Example 11</b><br>(mixture of enantiomers) |                                | Intermediate 12  | 321                    | 3.10                   |
| <b>Example 12</b>                             |                                | Cyclopropyl amine                                      | 275                    | 2.98                   |

5

**Example 13:** Ethyl 4-[(1,1-dioxidotetrahydrothien-3-yl)amino]-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate



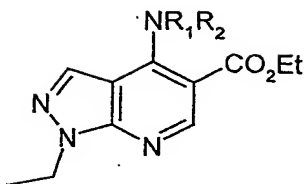
Example 13 NR<sub>1</sub>R<sub>2</sub> =

10

Intermediate 1 (0.05g) and Intermediate 13 (0.027g) were suspended in ethanol (1ml) and triethylamine (0.14ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 24h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between DCM (2ml) and water (1.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a gradient of EtOAc : cyclohexane; (1:8 then 1:4, 1:2, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Example 13 (0.045g) as a mixture of enantiomers. LCMS showed MH<sup>+</sup> = 353; T<sub>RET</sub> = 2.60min.

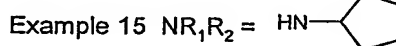
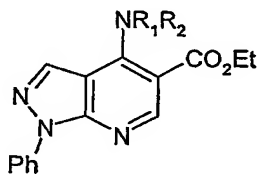
20

Similarly prepared was the following:



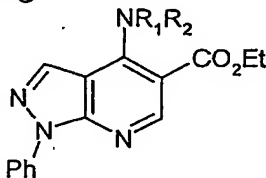
|                   | NR <sub>1</sub> R <sub>2</sub> | Amine Reagent   | MH <sup>+</sup><br>ion | T <sub>RET</sub> (min) |
|-------------------|--------------------------------|-----------------|------------------------|------------------------|
| <b>Example 14</b> |                                | Intermediate 14 | 367                    | 2.64                   |

5 **Example 15:** Ethyl 4-(cyclopentylamino)-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

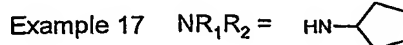
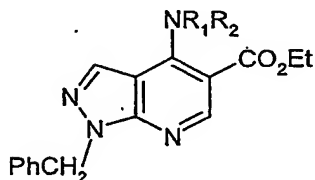


10 Intermediate 5 (0.02g) and cyclopentyl amine (0.007ml) were suspended in ethanol (1ml) and triethylamine (0.046ml) was added. The mixture was stirred under nitrogen and heated at 80°C for 18h. After cooling to room temperature, ethanol was removed by evaporation under a stream of nitrogen and the residue partitioned between chloroform (1ml) and water (0.5ml). The layers were separated and the organic layer concentrated to dryness. Purification was carried out using an SPE cartridge (silica, 5g), eluting with a  
15 gradient of Et<sub>2</sub>O : cyclohexane; (0:1 then 1:8, 1:5, 1:3, 1:1 and 1:0). Fractions containing desired material were combined and concentrated in vacuo to afford Example 15 (0.024g). LCMS showed MH<sup>+</sup> = 351; T<sub>RET</sub> = 4.19min.

Similarly prepared was the following:

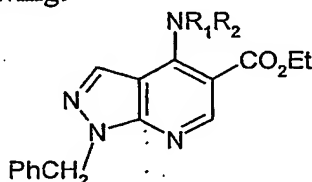


| NR <sub>1</sub> R <sub>2</sub> | Amine Reagent           | Product    | MH <sup>+</sup> ion | T <sub>RET</sub> (min) |
|--------------------------------|-------------------------|------------|---------------------|------------------------|
|                                | 4-Amino tetrahydropyran | Example 16 | 367                 | 3.58                   |

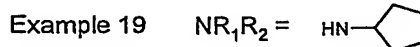
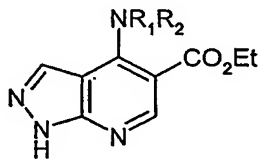
**Example 17: Ethyl 4-(cyclopentylamino)-1-benzyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**

- 5 Intermediate 4 (0.04g) was placed in a Reactivial™ and treated with cyclopentyl amine (0.05ml). The mixture was heated at 90°C for 1.5h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated, then applied as a solution in chloroform to a preparative TLC plate (silica, 20cm x 20cm x 1mm) which was eluted with ethyl acetate : petrol (1:2). The required band was removed from the plate and the silica washed with ethyl acetate (2 x 15ml). Concentration of the ethyl acetate solution *in vacuo* afforded Example 17 as a white solid (0.013g). LCMS showed  $MH^+ = 365$ ;  $T_{RET} = 3.69$  min.

- 15 Similarly prepared was the following:



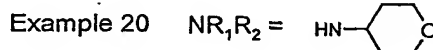
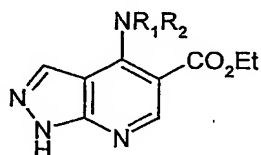
|                   | $NR_1R_2$ | Amine reagent           | $MH^+$ ion | $T_{RET}(\text{min})$ |
|-------------------|-----------|-------------------------|------------|-----------------------|
| <b>Example 18</b> |           | 4-Amino tetrahydropyran | 381        | 3.28                  |

**Example 19: Ethyl 4-(cyclopentylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**

- 20 Intermediate 2 (0.035g) was placed in a Reactivial™ and treated with cyclopentyl amine (0.05ml). The mixture was heated at 90°C for 1.5h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated. The residual solid was triturated with
- 25

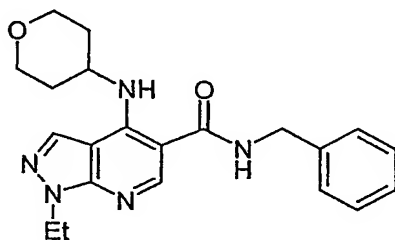
Et<sub>2</sub>O and the insoluble off-white solid collected and air-dried to afford Example 19 (0.016g). LCMS showed MH<sup>+</sup> = 275; T<sub>RET</sub> = 2.58 min.

5 **Example 20: Ethyl 4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate**

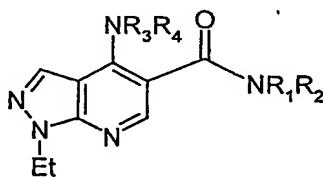


10 Intermediate 2 (0.035g) was placed in a Reactival™ and treated with 4-aminotetrahydropyran (0.05ml). The mixture was heated at 90°C for 1.5h, then allowed to cool to room temperature and partitioned between chloroform (2ml) and water (1ml). The layers were separated and the organic phase was concentrated. The crude product was purified by mass directed autoprep HPLC to afford Example 20 as an off-white solid (0.011g). LCMS showed MH<sup>+</sup> = 291; T<sub>RET</sub> = 2.08 min.

15 **Example 21: N-benzyl-1-ethyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide**



that is, Example 21 is:



wherein NR<sub>1</sub>R<sub>2</sub> =

NR<sub>3</sub>R<sub>4</sub> =

20 Three alternative methods, A, B and C, have been used to make Example 21, as follows:

**Example 21, Method A:**

25 A solution of the 4-chloro Intermediate 17 (0.031g, 0.1 mmol) in ethanol (1.9ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of 4-aminotetrahydropyran (Intermediate 8, 1.1ml of the 0.1M ethanolic solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion of 4-amino-



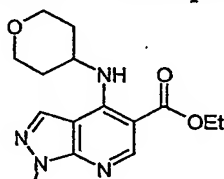
- tetrahydropyran (0.01ml of undiluted amine, not a solution thereof) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in dichloromethane (DCM), then applied to an solid phase extraction (SPE) cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol.
- 5 Fractions containing desired material were concentrated in vacuo to afford Example 21 (0.004g). LCMS showed  $MH^+ = 380$ ;  $T_{RET} = 2.92$ min.

**Example 21, Method B:**

- Intermediate 17 (0.031g, 0.1 mmol) was dissolved in acetonitrile (1ml).
- 10 4-Aminotetrahydropyran hydrochloride (Intermediate 8A, 0.015g, 0.11 mmol) and N,N-diisopropylethylamine (0.08ml, 0.5 mmol) were added and the mixture stirred under nitrogen at 85°C for 16h, then concentrated in vacuo. The residue was partitioned between dichloromethane (DCM) and water. The layers were separated and the organic layer was concentrated in vacuo to afford Example 21 (0.027g). LCMS showed  $MH^+ =$
- 15 380;  $T_{RET} = 2.92$  min.

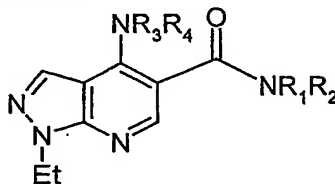
**Example 21, Method C:**

This alternative route C to Example 21 involves formation of the ester of Example 3 =

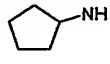
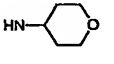
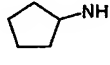
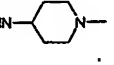
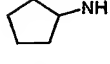
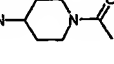

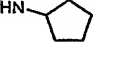

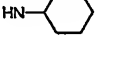

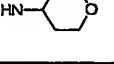
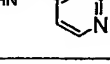
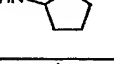
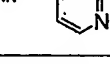

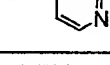
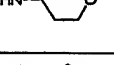
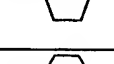
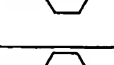
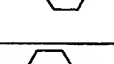
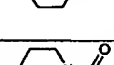
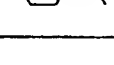


- Intermediate 32 ( ) using one of the methods described above,
- 20 conversion of the ester of Example 3 / Intermediate 32 into the carboxylic acid (Intermediate 33) using the method given above for Intermediate 33, and then amide bond formation to form Example 21 using the method of Examples 81-84 below.

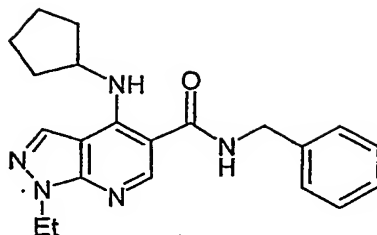
- The following compounds can be similarly prepared using one or more of Methods A, B
- 25 or C above, preferably Method A or B:



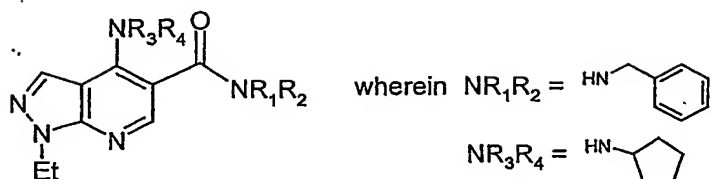
|            | NR1R2 | NR3R4 | Starting Material | Amine Reagent           | $MH^+$ ion | $T_{RET}$ (min) |
|------------|-------|-------|-------------------|-------------------------|------------|-----------------|
| Example 22 |       |       | Intermediate 19   | 4-amino tetrahydropyran | 384        | 3.09            |
| Example 23 |       |       | Intermediate 20   | Cyclopentyl amine       | 342        | 3.29            |
| Example 24 |       |       | Intermediate 20   | Cyclohexyl amine        | 356        | 3.47            |

|                   |   |   |                 |                         |     |      |
|-------------------|---|---|-----------------|-------------------------|-----|------|
| <b>Example 25</b> |  |    | Intermediate 20 | 4-amino tetrahydropyran | 358 | 2.79 |
| <b>Example 26</b> |  |    | Intermediate 20 | Intermediate 7          | 371 | 2.16 |
| <b>Example 27</b> |  |    | Intermediate 20 | Intermediate 6          | 400 | 2.64 |
| <b>Example 28</b> |  |    | Intermediate 21 | Cyclopentyl amine       | 328 | 2.69 |
| <b>Example 29</b> |  |    | Intermediate 21 | Cyclohexyl amine        | 342 | 2.87 |
| <b>Example 30</b> |  |    | Intermediate 21 | 4-amino tetrahydropyran | 344 | 2.33 |
| <b>Example 31</b> |  |    | Intermediate 22 | Cyclopentyl amine       | 365 | 2.38 |
| <b>Example 32</b> |  |    | Intermediate 22 | Cyclohexyl amine        | 379 | 2.54 |
| <b>Example 33</b> |  |    | Intermediate 22 | 4-amino tetrahydropyran | 381 | 2.09 |
| <b>Example 34</b> | NH <sub>2</sub>   |  | Intermediate 24 | Cyclopentyl amine       | 274 | 2.59 |
| <b>Example 35</b> | NH <sub>2</sub>   |  | Intermediate 24 | Cyclohexyl amine        | 288 | 2.79 |
| <b>Example 36</b> | NH <sub>2</sub>   |  | Intermediate 24 | 4-amino tetrahydropyran | 290 | 2.22 |
| <b>Example 37</b> | NH <sub>2</sub>   |  | Intermediate 24 | Intermediate 7          | 303 | 1.81 |
| <b>Example 38</b> | NH <sub>2</sub>   |  | Intermediate 24 | Intermediate 6          | 332 | 2.06 |

**Example 39:** N-Benzyl-4-(cyclopentylamino)-1-ethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

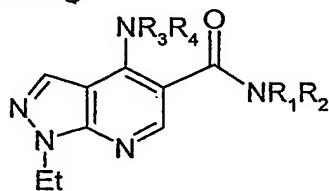


that is, Example 39 is:



A solution of Intermediate 17 (0.031g, 0.1 mmol) in ethanol (1ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of cyclopentyl amine (1.1ml of the 0.1M ethanolic solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion of cyclopentyl amine (0.009ml of undiluted amine, not a solution thereof) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in DCM, then applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. The DCM fraction was concentrated in vacuo, then applied to an SPE cartridge (silica, 0.5g) which was eluted sequentially with (i) DCM, (ii) Et<sub>2</sub>O, (iii) EtOAc and (iv) MeOH. Fractions containing desired material were combined to afford Example 39 (0.007g). LCMS showed MH<sup>+</sup> = 364; T<sub>RET</sub> = 3.38min.

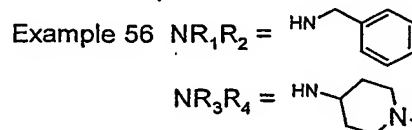
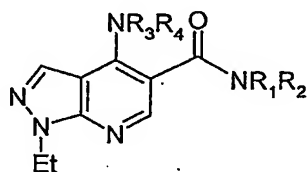
Similarly prepared were the following:



|            | NR <sub>1</sub> R <sub>2</sub> | NR <sub>3</sub> R <sub>4</sub> | Starting Material | Amine reagent     | MH <sup>+</sup> ion | T <sub>RET</sub> (min) |
|------------|--------------------------------|--------------------------------|-------------------|-------------------|---------------------|------------------------|
| Example 40 |                                |                                | Intermediate 17   | Cyclohexyl amine  | 378                 | 3.43                   |
| Example 41 |                                |                                | Intermediate 17   | Intermediate 6    | 422                 | 2.75                   |
| Example 42 |                                |                                | Intermediate 18   | Cyclopentyl amine | 358                 | 3.63                   |
| Example 43 |                                |                                | Intermediate 18   | Cyclohexyl amine  | 372                 | 3.79                   |

|            |  |  |                 |                          |     |      |
|------------|--|--|-----------------|--------------------------|-----|------|
| Example 44 |  |  | Intermediate 18 | 4-amino tetrahydro-pyran | 374 | 3.13 |
| Example 45 |  |  | Intermediate 18 | Intermediate 7           | 387 | 2.37 |
| Example 46 |  |  | Intermediate 18 | Intermediate 6           | 416 | 2.92 |
| Example 47 |  |  | Intermediate 19 | Cyclopentyl amine        | 368 | 3.61 |
| Example 48 |  |  | Intermediate 19 | Cyclohexyl amine         | 382 | 3.76 |
| Example 49 |  |  | Intermediate 19 | Intermediate 7           | 397 | 2.29 |
| Example 50 |  |  | Intermediate 19 | Intermediate 6           | 426 | 2.88 |
| Example 51 |  |  | Intermediate 23 | Cyclopentyl amine        | 316 | 3.05 |
| Example 52 |  |  | Intermediate 23 | Cyclohexyl amine         | 330 | 3.26 |
| Example 53 |  |  | Intermediate 23 | 4-amino tetrahydro-pyran | 332 | 2.58 |
| Example 54 |  |  | Intermediate 23 | Intermediate 7           | 345 | 1.94 |
| Example 55 |  |  | Intermediate 23 | Intermediate 6           | 374 | 2.46 |

**Example 56:** N-Benzyl-1-ethyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



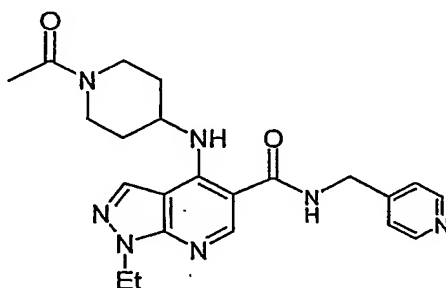
5

A solution of Intermediate 17 (0.031g, 0.1 mmol) in ethanol (1ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of Intermediate 7 (1.1ml of the solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h. A further portion Intermediate 7 (0.01ml of undiluted amine) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in DCM, then applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with

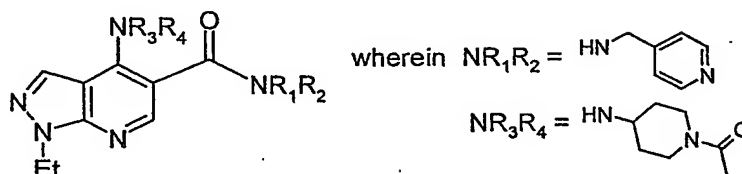
10

DCM, then with methanol. The DCM fraction was concentrated in vacuo, then applied to an SPE cartridge (silica, 0.5g) which was eluted sequentially with (i) DCM, (ii) Et<sub>2</sub>O, (iii) EtOAc and (iv) MeOH. The methanol fraction was concentrated and further purified by SPE (silica, 0.5g) eluting with (i) DCM, (ii) EtOAc and (iii) a stepwise gradient of chloroform : methanol (from 99:1 up to 4:1). Fractions containing desired material were combined to afford Example 56 (0.004g). LCMS showed MH<sup>+</sup> = 393; T<sub>RET</sub> = 2.26min.

**Example 57:** 4-[(1-Acetylpiperidin-4-yl)amino]-1-ethyl-N-(pyridin-4-ylmethyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



that is, Example 57 is:

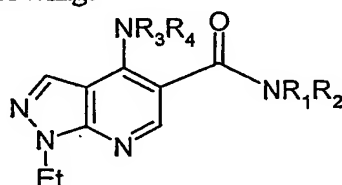


A solution of Intermediate 22 (0.03g, ca. 0.1 mmol) in ethanol (1ml) was treated with triethylamine (0.07ml, 0.5 mmol), followed by a 0.1M ethanolic solution of Intermediate 6 (1.1ml of the solution = 0.11 mmol). The mixture was heated at reflux (80°C) for 18h.

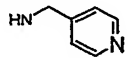
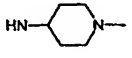

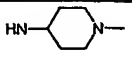

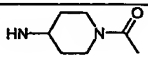
A further portion of Intermediate 6 (0.01ml, undiluted) was then added and heating continued for a further 24h. Volatiles were removed in vacuo and the residue dissolved in DCM, then applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol.

The DCM fraction was concentrated in vacuo, then applied to an SPE cartridge (silica, 0.5g) eluting with (i) DCM, (ii) EtOAc and (iii) a stepwise gradient of chloroform : methanol (from 99:1 up to 4:1). Fractions containing desired material were combined to afford Example 57 (0.003g). LCMS showed MH<sup>+</sup> = 423; T<sub>RET</sub> = 2.1min.

Similarly prepared were the following:

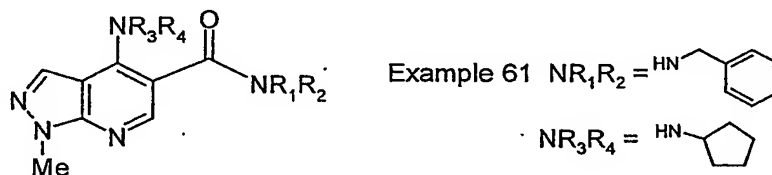


|  | NR <sub>1</sub> R <sub>2</sub> | NR <sub>3</sub> R <sub>4</sub> | Starting | Amine | MH <sup>+</sup> | T <sub>RET</sub> |
|--|--------------------------------|--------------------------------|----------|-------|-----------------|------------------|
|--|--------------------------------|--------------------------------|----------|-------|-----------------|------------------|

|            |   |   | Material        | reagent        | ion | (min) |
|------------|---|---|-----------------|----------------|-----|-------|
| Example 58 |  |  | Intermediate 22 | Intermediate 7 | 394 | 1.66  |
| Example 59 |  |  | Intermediate 21 | Intermediate 7 | 387 | 1.94  |
| Example 60 |  |  | Intermediate 21 | Intermediate 6 | 386 | 2.3   |

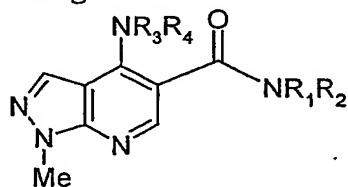
**Example 61: N-Benzyl-4-(cyclopentylamino)-1-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxamide**

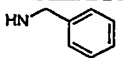
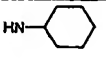
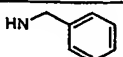
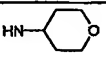
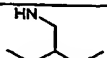
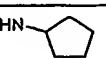
5

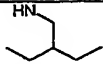
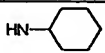
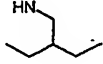
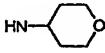
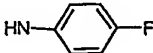
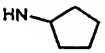
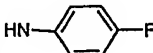
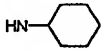
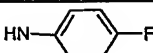
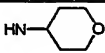
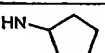

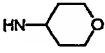


A solution of Intermediate 28 (0.03g, 0.1 mmol) in ethanol (1ml) was treated with a 0.1M ethanolic solution of cyclopentyl amine (1.1ml of solution = 0.11 mmol). Triethylamine (0.07ml, 0.5 mmol) was then added and the mixture heated at reflux (85°C), under nitrogen for 12h. A further portion of cyclopentyl amine (0.009ml, undiluted) was then added and heating continued for a further 36h. The mixtures were concentrated in vacuo and the residue treated with chloroform. A small amount of insoluble material was collected by filtration, then the filtrate applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. Fractions containing desired material were combined to afford Example 61 (0.039g). LCMS showed  $MH^+ = 350$ ;  $T_{RET} = 2.88\text{min}$ .

Similarly prepared were the following:

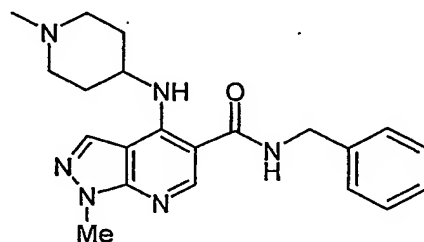


|            | NR1R2   | NR3R4   | Starting Material | Amine Reagent           | MH + ion | T <sub>RET</sub> (min) |
|------------|---|---|-------------------|-------------------------|----------|------------------------|
| Example 62 |  |  | Intermediate 28   | Cyclohexyl amine        | 364      | 3.05                   |
| Example 63 |  |  | Intermediate 28   | 4-amino tetrahydropyran | 366      | 2.52                   |
| Example 64 |  |  | Intermediate 29   | Cyclopentyl             | 344      | 3.06                   |

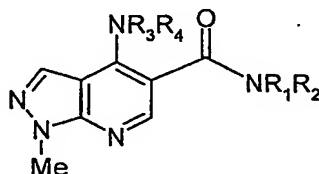
|            |   |   |                 |                         |     |      |
|------------|---|---|-----------------|-------------------------|-----|------|
|            |   |   |                 | amine                   |     |      |
| Example 65 |  |  | Intermediate 29 | Cyclohexyl amine        | 358 | 3.23 |
| Example 66 |  |  | Intermediate 29 | 4-amino tetrahydropyran | 360 | 2.69 |
| Example 67 |  |  | Intermediate 30 | Cyclopentyl amine       | 354 | 3.17 |
| Example 68 |  |  | Intermediate 30 | Cyclohexyl amine        | 368 | 3.33 |
| Example 69 |  |  | Intermediate 30 | 4-amino tetrahydropyran | 370 | 2.72 |
| Example 70 | NH <sub>2</sub>   |  | Intermediate 31 | Cyclopentyl amine       | 260 | 2.10 |
| Example 71 | NH <sub>2</sub>   |  | Intermediate 31 | Cyclohexyl amine        | 274 | 2.29 |
| Example 72 | NH <sub>2</sub>   |  | Intermediate 31 | 4-amino tetrahydropyran | 276 | 1.86 |

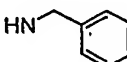
**Example 73:** N-Benzyl-1-methyl-4-[(1-methylpiperidin-4-yl)amino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

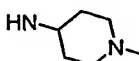
5



that is, Example 73 is:



wherein  $NR_1R_2 =$  

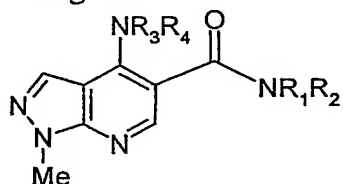
$NR_3R_4 =$  

10

A solution of Intermediate 28 (0.03g, 0.1 mmol) in ethanol (1ml) was treated with a 0.1M ethanolic solution of Intermediate 7 (1.1ml of solution = 0.11 mmol). Triethylamine (0.07ml, 0.5 mmol) was then added and the mixture heated at reflux (85°C), under nitrogen for 12h. A further portion of Intermediate 7 (0.01ml, undiluted) was then added and heating continued for a further 36h. The mixtures were concentrated in vacuo and the residue treated with chloroform. A small amount of insoluble material was collected by

filtration, then the filtrate applied to an SPE cartridge (aminopropyl, 1g) which was eluted first with DCM, then with methanol. Fractions containing desired material were combined and concentrated in vacuo. The residue was further purified by SPE (silica, 0.5g) eluting with (i) DCM, (ii) chloroform, (iii) EtOAc and (iv) a stepwise gradient of chloroform : methanol (from 99:1 up to 4:1). Fractions containing desired material were combined to afford Example 73 (0.029g). LCMS showed  $MH^+ = 379$ ;  $T_{RET} = 2.05$ min.

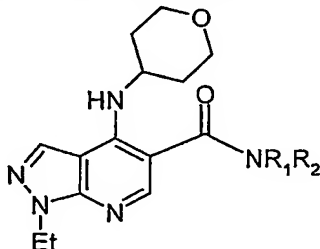
Similarly prepared were the following:



|            | NR1R2           | NR3R4 | Starting Material | Amine Reagent  | MH <sup>+</sup> ion | T <sub>RET</sub> (min) |
|------------|-----------------|-------|-------------------|----------------|---------------------|------------------------|
| Example 74 |                 |       | Intermediate 28   | Intermediate 6 | 407                 | 2.57                   |
| Example 75 |                 |       | Intermediate 29   | Intermediate 7 | 373                 | 2.20                   |
| Example 76 |                 |       | Intermediate 29   | Intermediate 6 | 401                 | 2.74                   |
| Example 77 |                 |       | Intermediate 30   | Intermediate 7 | 383                 | 2.12                   |
| Example 78 |                 |       | Intermediate 30   | Intermediate 6 | 411                 | 2.69                   |
| Example 79 | NH <sub>2</sub> |       | Intermediate 31   | Intermediate 7 | 289                 | 1.64                   |
| Example 80 | NH <sub>2</sub> |       | Intermediate 31   | Intermediate 6 | 317                 | 1.99                   |

10

**Example 81: 1-Ethyl-N-methyl-4-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide**



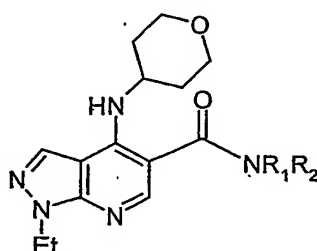
Example 81  $NR_1R_2 = NHMe$

15



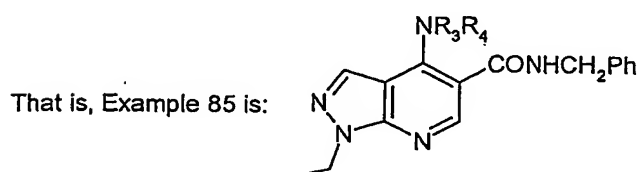
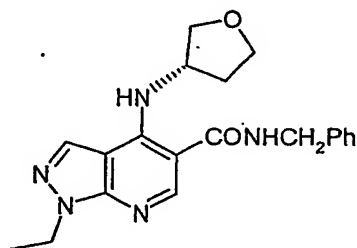
To a stirred suspension of Intermediate 33 (0.025g, ca. 0.08 to 0.09 mmol) in chloroform (2ml) was added thionyl chloride (0.025ml) and the mixture stirred at room temperature for 1h. The mixture was cooled to 0°C and methylamine added (2M solution in THF, 0.69ml = 1.38 mmol). After returning to room temperature the mixture was stirred for a further 1h, then quenched by addition of water (4ml) and the layers separated. The organic layer was concentrated then applied to an SPE cartridge (silica, 1g) which was eluted with (i) DCM, (ii) Et<sub>2</sub>O (2:1), (iii) EtOAc, (iv) MeOH: EtOAc (1:9). Fractions containing desired material were combined to afford Example 81 (0.019g). LCMS showed MH<sup>+</sup> = 304; T<sub>RET</sub> = 2.19min.

Similarly prepared:



|            | NR1R2              | Amine reagent              | MH <sup>+</sup><br>ion | T <sub>RET</sub><br>(min) |
|------------|--------------------|----------------------------|------------------------|---------------------------|
| Example 82 | NMe <sub>2</sub>   | Dimethylamine (2M in THF)  | 318                    | 2.06                      |
| Example 83 | NHEt               | Ethylamine (2M in THF)     | 318                    | 2.31                      |
| Example 84 | NH <sup>i</sup> Pr | Isopropylamine (2M in THF) | 332                    | 2.44                      |

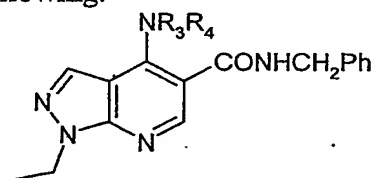
15 **Example 85:** N-Benzyl-1-ethyl-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide



wherein NR<sub>3</sub>R<sub>4</sub> =

Intermediate 41 (0.017g, 0.062 mmol) was dissolved in DMF (2ml), then treated with HATU (0.023g) followed by diisopropylethyl amine (0.021ml) and the mixture stirred for 10 min. Benzylamine (0.007ml) was then added and stirring continued for a further 64h. The mixture was concentrated in vacuo and the residue dissolved in DCM (1.5ml) then treated with saturated aqueous sodium bicarbonate solution (1.5ml). This mixture was stirred for 30 min, then the layers were separated and the organic layer was applied to an SPE cartridge (silica, 1g) which was eluted sequentially with a gradient of ethyl acetate: cyclohexane (1:4, then 1:2, 1:1, 2:1 and 1:0). Fractions containing desired material were concentrated in vacuo to afford Example 85 (0.017g). LCMS showed  $MH^+ = 366$ ;  $T_{RET} = 2.80$ min.

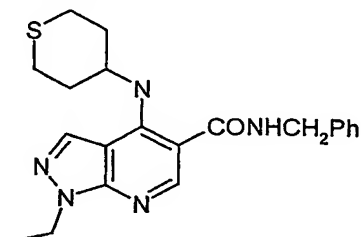
Similarly prepared were the following:



|                   | $NR_3R_4$ | Starting material | $MH^+$<br>ion | $T_{RET}$<br>(min) |
|-------------------|-----------|-------------------|---------------|--------------------|
| <b>Example 86</b> |           | Intermediate 42   | 366           | 2.80               |
| <b>Example 87</b> |           | Intermediate 44   | 382           | 3.11               |
| <b>Example 88</b> |           | Intermediate 45   | 336           | 3.00               |
| <b>Example 89</b> |           | Intermediate 46   | 414           | 2.69               |
| <b>Example 90</b> |           | Intermediate 47   | 428           | 2.75               |

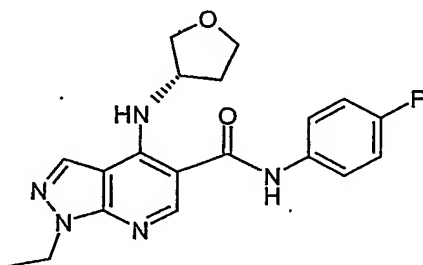
15

**Example 91:** N-Benzyl-1-ethyl-4-(tetrahydro-2H-thiopyran-4-ylamino)-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

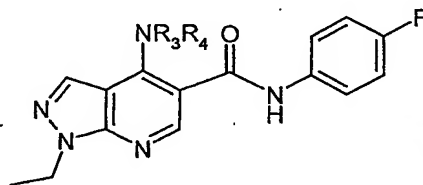


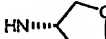
Intermediate 43 (0.019g) was dissolved in DMF (2ml), then treated with HATU (0.024g) followed by diisopropylethyl amine (0.022ml) and the mixture stirred for 10 min. Benzylamine (0.007ml) was then added and stirring continued for a further 64h. The mixture was concentrated in vacuo and the residue dissolved in DCM (1.5ml) then treated with saturated aqueous sodium bicarbonate solution (1.5ml). This mixture was stirred for 30 min, then the layers were separated and the organic layer applied to an SPE cartridge (silica, 1g) which was eluted sequentially with a gradient of ethyl acetate: cyclohexane (1:4, then 1:2, 1:1 and 1:0). Fractions containing desired material were concentrated in vacuo to afford Example 91 (0.023g). LCMS showed  $MH^+ = 396$ ;  $T_{RET} = 3.26$ min.

**Example 92: 1-Ethyl-N-(4-fluorophenyl)-4-[(3S)-tetrahydrofuran-3-ylamino]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide**



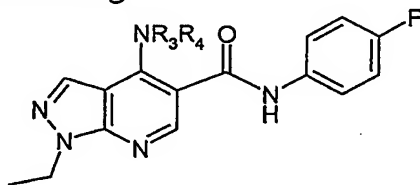
that is, Example 92 is:



wherein  $NR_3R_4 =$  

Intermediate 41 (0.017g) was dissolved in DMF (2ml), then treated with HATU (0.023g) followed by diisopropylethyl amine (0.021ml) and the mixture stirred for 10 min. 4-Fluoroaniline (0.006ml) was then added and stirring continued for a further 64h. The mixture was concentrated in vacuo and the residue dissolved in DCM (1.5ml) then treated with saturated aqueous sodium bicarbonate solution (1.5ml). This mixture was stirred for 30 min, then the layers were separated and the organic layer concentrated in vacuo. The crude mixture was purified by mass directed autoprep HPLC to afford Example 92 (0.013g). LCMS showed  $MH^+ = 370$ ;  $T_{RET} = 2.91$ min.

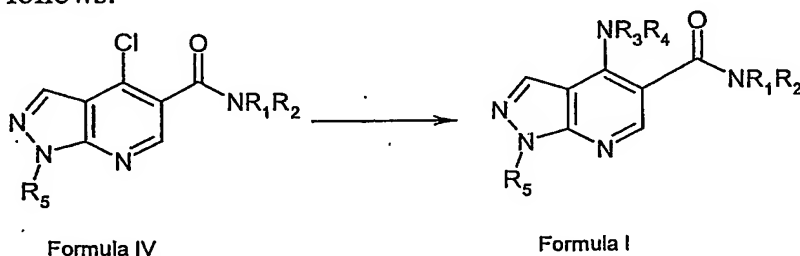
Similarly prepared were the following:



|                   | NR <sub>3</sub> R <sub>4</sub> | Starting material | MH <sup>+</sup><br>ion | T <sub>RET</sub><br>(min) |
|-------------------|--------------------------------|-------------------|------------------------|---------------------------|
| <b>Example 93</b> |                                | Intermediate 42   | 370                    | 2.91                      |
| <b>Example 94</b> |                                | Intermediate 43   | 400                    | 3.37                      |
| <b>Example 95</b> |                                | Intermediate 44   | 386                    | 3.27                      |
| <b>Example 96</b> |                                | Intermediate 45   | 340                    | 3.21                      |
| <b>Example 97</b> |                                | Intermediate 46   | 418                    | 2.80                      |
| <b>Example 98</b> |                                | Intermediate 47   | 432                    | 2.84                      |

**Example 99**

- 5 In all of Examples 22 to 98, where a 4-amino 5-carboxamide Example of the following Formula I has been synthesised from the 4-chloro derivative, then an alternative final-step synthesis is as follows:



- 10 An intermediate of Formula IV above (0.1mmol) was dissolved in acetonitrile (1ml). An amine of formula HR<sub>3</sub>R<sub>4</sub> (0.1mmol, preferably wherein one of R<sub>4</sub> and R<sub>3</sub> = H) and N,N-diisopropylethylamine (0.5mmol) were added and the mixture stirred under nitrogen at 85°C for 16h. After concentration in vacuo, the residue was partitioned between dichloromethane (DCM) and water. The layers were separated and the organic layer was
- 15 concentrated in vacuo to afford an Example of Formula I.